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APPLICATION

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on

CRYSTAL STRUCTURE OF WW DOMAINS AND METHODS OF USE THEREOF

by

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CRYSTAL STRUCTURE OF WW DOMAINS AND METHODS OF USE THEREOF

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FIELD OF THE INVENTION

The present invention relates to crystals of WW domains and more particularly to the high resolution structure of Pin1 WW domain obtained by X-ray diffraction. In addition, the invention relates to methods of using the structure coordinates of Pin1 WW domain and mutants thereof to screen and design compounds that bind to or interact with WW domains.

BACKGROUND

The process of designing potent and specific inhibitors has improved with the arrival of techniques for determining the three-dimensional structure of the enzyme to be inhibited. Usually a three-dimensional model of an enzyme is produced by the creation of a crystalline form of the purified enzyme which is then subjected to X-ray diffraction and analysis. While such procedures provide certain valuable information that can be used to design inhibitors, they suffer from a lack of knowledge about the amino acid residues critical for interaction with a substrate or a substrate mimic. In order to address these limitations, enzymes have more recently been co-crystallized with substrates, substrate mimics or known inhibitors of the enzyme's activity, thereby allowing the important interactions to be determined (see, for example, Mohammadi, *et al.*, Science 276:955-960, 1997; Lee, *et al.*, Biochemistry 36:13180-13186, 1997; Brzozowski, *et al.*, Nature 389:753-758, 1997).

The peptidyl-prolyl *cis*-trans isomerases (PPIases), or rotamases, are a family of enzymes important in protein folding, assembly and transport. They act as catalysts to promote isomerization about the peptidyl-prolyl bond, which can have profound effects on protein function.

PPIases are divided into three classes, cyclophilins, FK-506 binding proteins (FKBPs) and the Pin1/parvulin class. While cyclophilins and FKBPs are

distinguished by their ability to bind immunosuppressant molecules cyclosporin and FK-506, respectively, the Pin1/parvulin class binds neither of these immunosupressants and is structurally unrelated to the other two classes. Known members of the Pin1/parvulin class include Pins 1 - 3 (Lu, *et al.*, Nature 380:544-547, 1996), Pin-L (Campbell, *et al.*, Genomics 44:157-162, 1997), parvulin (Rahfeld, *et al.*, FEBS Letts 352:180-184, 1994), dodo (Maleszka, *et al.*, Proc Natl Acad Sci USA 93:447-451, 1996) and Ess1/Pft1 (Hanes, *et al.*, Yeast 5:55-72, 1989; and Hani, *et al.*, FEBS Letts 365:198-202, 1995).

Recent research suggests that members of the Pin1/parvulin class are essential modulators of the cell cycle, and mitosis in particular. Lu, *et al.*, Nature 380:544-547, 1996 (incorporated by reference herein) reports that depletion of Pin1/Ess1 (a structural and functionally related protein to Pin1) in yeast or human cells induces mitotic arrest followed by apoptosis, indicating that enzymes in this class serve an essential function in cell division and proliferation.

The design of new, highly specific antimitotic agents represents an important need in the pharmaceutical industry. Such agents can serve as effective chemotherapeutic agents for the treatment of a variety of disorders characterized by inappropriate cell proliferation, including cancer and infectious diseases. The invention disclosed herein addresses this and related needs, as will become apparent upon review of the specification and appended claims.

SUMMARY OF THE INVENTION

A Pin1 WW domain crystal structure is provided. Methods of using the crystal structure and atomic coordinates for the development of WW domain binding agents is also provided. In addition, the disclosure provides computer programs on computer readable medium for use in developing WW domain binding agents.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 collectively shows the overall architecture of human Pin1.

Figure 1A shows the ribbon representation of the Pin1-C-Terminal Domain (CTD) peptide complex. Residues 39 to 50 are disordered. Apostrophes distinguish the WW

domain from the PPIase domain. The CTD peptide backbone is in the region labeled as N, Pro3' and Pro6'. Residues of the CTD peptide are labeled with apostrophes. Atoms of carbon, nitrogen, phosphorus, oxygen, and sulfur are depicted. Dotted lines depict hydrogen bonds. **Figure 1B** shows a ribbon representation of the Pin1-PEG complex.

Figure 2 collectively shows an enlarged view of the Pin1-CTD peptide binding interface. **Figure 2A** shows a ribbon diagram of the Pin1 WW domain bound to YpSPTpSPS depicted after a 90° rotation around a vertical axis from the view shown in **Figure 1A**. This view is looking on the concave WW domain peptide-binding surface opposite the PPIase domain. The carbon atoms of the CTD peptide are in the foreground compared to the WW side chain atoms. The water molecule mediating Tyr-23 / phosphate contacts is shown as a sphere. Hydrogen bonds are shown as dotted spheres. **Figure 2B** shows the molecular surface representation of the WW domain - peptide interface after a slight rotation around the vertical axis from the view depicted in **Figure 2A** affords this view. The solvent-accessible surface for the Pin1 WW domain residues was calculated in GRASP (Nicholls *et al.*, Proteins 11:281-296, 1991), and the acidic and basic residues depicted as the darker regions adjacent to Lys6, Glu35, Arg36, Arg21, and Arg17.

Figure 3 shows a schematic and energetic view of the Pin1-YpSPTpSPS complex. Pin1 residues are towards the bottom of the figure and are not covalently linked to the larger molecule which represents CTD. Residues participating in van der Waals contacts are highlighted with gray and the extended van der Waals surfaces appear as dotted gray curves. Hydrogen bonds are shown as dashed lines. In the case of the S16H and W34H mutants, some of the apparent binding is likely being contributed by the PPIase domain. Residues are given as single letter codes.

Figure 4 collectively shows representative WW domains. **Figure 4A** shows the sequence alignment of 15 WW domains. The secondary structural elements are those of Pin1. The numbers correspond to the first residue on each line for each of the fifteen WW domains. The Darker gray boxes delineate residues participating in phosphate contacts. Shaded boxes corresponding to residues 23 and 24 define

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residues participating in van der Waals contacts with Pro-3' of the CTD peptide. Shaded residues 14 and 25 contribute to the van der Waals surface sequestering the backbone of residues 4' to 6' as well as the Pro ring of Pro-6'. Light gray boxes corresponding to residue 32 define residues participating in additional hydrogen bonds with the CTD peptide. Residues participating in more then one class of interactions are outlined and coded as described above. h is human, Sc is *Saccharomyces cerevisiae*, d is *Drosophila*, m is mouse, and En is *Emericella nidulans*. **Figure 4B** shows stereo views of the Cα traces of the Pin1-YpSPTpSPS complex (top) and the YAP65-PPXY peptide complex (bottom) aligned with Pin1's WW domain. The figure is labeled as in previous figures. The backbones of the WW domains are now shown as coils. The arrow in the bottom panel depicts the movement necessary to bring the PPXY-containing peptide into alignment with the CTD peptide bound to Pin1. The numbering scheme for YAP65 refers to the human sequence. The numbers in parentheses correspond to the alternate numbering scheme used by Macias *et al.* (Nature 382:646-649, 1996).

Figure 5 is a block diagram of a computer system.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, methods of identifying WW domain binding agents are provided. Invention methods include defining an interaction site of a WW domain based on a plurality of atomic coordinates of the WW domain, modeling a potential binding agent that fits spatially into said interaction site, contacting said potential binding agent with the WW domain in the presence of a WW domain substrate, and determining the ability of the potential binding agent to compete with the WW domain substrate for binding to the WW domain.

In another aspect, the invention provides a computer program on a computer readable medium, said computer program having instructions to cause a computer to model a potential binding agent that fits spatially into a WW domain interaction site defined by a plurality of atomic coordinates.

WW domains

The WW domain is a 38-40 amino acid structural motif that functions as an interaction module in a diverse set of signaling proteins. The modular nature of WW domain interactions lends itself to classification into five distinct groups based upon current understanding of their binding specificity. Group I WW domains, exemplified by YAP65, recognize PPxY motifs2; Group II WW domains, like FE65, bind the PPLP motif. Group III WW domains, such as those found in a subset of FBPs, interact with PGM motifs. A fourth group represented by the WW domain of Pin1, specifically interact with phosphorylated serine or threonine residues amino-terminal to proline, or ^{phosphorylated}SER-PRO (P.Ser-Pro) or ^{phosphorylated}THR-PRO (P.Thr-Pro) motifs. Finally, the recently classified group V WW domains recognize PGR motifs. Pin1 contains an N-terminal WW domain and a C-terminal peptidyl-prolyl cis-trans isomerase domain connected by a flexible linker. Provided here are the functional and structural basis for WW domain binding to phosphorylated protein substrates based on the energetic and structural analysis of a Pin1-phosphopeptide complex.

Pin1 has been implicated in the regulation of a diverse set of mitotically phosphorylated proteins including Cdc25, Myt1, Wee1, Plk1, and Cdc27, and also Tau11. In addition, Pin1 and its homolog, Ess1p, have both been implicated in the regulation of the C-terminal domain (CTD) of RNA Polymerase II (Pol II) and they can both bind directly to the phosphorylated CTD. Phosphorylation of Ser-2' and/or Ser-5' on the multiple YSPTSPS heptad repeats in the CTD of Pol II by cyclin-dependent kinases (CDKs) converts Pol IIa to Pol IIo and initiates a cascade of transcriptional, processing, and splicing events linked to the elongating polymerase. Structural and functional analysis of Pin1 established that Pin1's PPIase domain (which belongs to the parvulin family of PPIases) catalyzes phosphorylation-dependent peptide bond isomerization in P.Ser-Pro segments. Finally, binding analyses demonstrate that the Pin1 WW domain acts as the predominant P.Ser/P.Thr-Pro binding motif.

One aspect of the invention resides in obtaining crystals of the WW domain of a Pin1 protein of sufficient quality to determine the three dimensional (tertiary) structure of the protein by X-ray diffraction methods. The knowledge obtained

concerning Pin1 WW domain proteins can be used in the determination of the three dimensional structure of the binding domain of other WW domain containing proteins (*e.g.*, Npw38 (Komuro *et al.*, Nucleic Acid Res. 27(9):1957-65, 1999). The binding domain can also be predicted by various computer models. Based on the structural coordinates of the WW domain (*i.e.*, the three dimensional protein structure of the binding domain), as described herein, small molecules which mimic the functional binding of a WW domain protein to its ligands can be designed and synthesized. Accordingly, in one embodiment, the invention provides a method of "rational" drug design. Another approach to "rational" drug design is based on a lead compound that is discovered using high throughput screens; the lead compound is further modified based on a crystal stucture of the binding regions of the molecule in question. Accordingly, another aspect of the invention is to provide starting materials for the rational design of drugs which prevent or mimic the action of a WW domain (e.g., Pin1 WW domain) protein binding to its ligand.

Pin1's amino acid sequence is known (Lu *et al.*, *supra*). The WW domain of Pin1 includes residues 1 to 39 and the PPIase domain includes residues 50-163 of Pin1. The term "amino acids" means the L-isomers of the naturally occurring amino acids or unnatural amino acids. The naturally occurring amino acids are glycine, alanine, valine, leucine, isoleucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagine, glutamic acid, glutamine, γ-carboxyglutamic acid, arginine, ornithine and lysine. Unless specifically indicated, all amino acids referred to in this application are in the L-form.

The term "unnatural amino acids" means amino acids that are not naturally found in proteins. Examples of unnatural amino acids used herein, include racemic mixtures of selenocysteine and selenomethionine. In addition, unnatural amino acids include the D or L forms of nor-leucine, para-nitrophenylalanine, homophenylalanine, para-fluorophenylalanine, 3-amino-2-benzylpropionic acid, homoarginine, and D-phenylalanine.

The term "positively charged amino acid" includes any naturally occurring or unnatural amino acid having a positively charged side chain under normal

physiological conditions. Examples of positively charged naturally occurring amino acids are arginine, lysine and histidine.

The term "negatively charged amino acid" includes any naturally occurring or unnatural amino acid having a negatively charged side chain under normal physiological conditions. Examples of negatively charged naturally occurring amino acids are aspartic acid and glutamic acid.

The term "hydrophobic amino acid" means any amino acid having an uncharged, nonpolar side chain that is relatively insoluble in water. Examples of naturally occurring hydrophobic amino acids are alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine.

The term "hydrophilic amino acid" means any amino acid having an uncharged, polar side chain that is relatively soluble in water. Examples of naturally occurring hydrophilic amino acids are serine, threonine, tyrosine, asparagine, glutamine, and cysteine.

The term "crystal structure coordinates" refers to mathematical coordinates derived from mathematical equations related to the patterns obtained on diffraction of a monochromatic beam of X-rays by the atoms (scattering centers) of a protein molecule in crystal form. The diffraction data are used to calculate an electron density map of the repeating unit of the crystal. The electron density maps are used to establish the positions of the individual atoms within the unit cell of the crystal. The crystal structure coordinates of the Pin1 protein binding domain (*e.g.*, the WW domain) are obtained from a Pin1 protein crystal having orthorhombic space group symmetry $P2_12_12_1$ with a = 35.27 Å, b = 43.90 Å, c = 124.66 Å, $\alpha = \beta = \gamma = 90^\circ$. The coordinates of the Pin1 protein binding domain can also be obtained by means of computational analysis.

The term "selenomethione substitution" refers to the method of producing a chemically modified form of a crystal of Pin1. The Pin1 protein is expressed by bacteria in media that is depleted in methionine and supplemented with selenomethionine. Selenium is thereby incorporated into the crystal in place of

methionine sulfurs. The location(s) of selenium are determined by X-ray diffraction analysis of the crystal. This information is used to generate the phase information used to construct a three-dimensional structure of the protein.

The term "heavy atom derivatization" refers to the method of producing a chemically modified form of the crystal of Pin1. A crystal is soaked in a solution containing heavy metal atom salts or organometallic compounds, which can diffuse through the crystal and bind to the surface of the protein. The location(s) of the bound heavy metal atom(s) are determined by X-ray diffraction analysis of the soaked crystal. This information is used to generate the phase information used to construct a three-dimensional structure of the protein.

The term "unit cell" refers to the basic parallelipiped shaped block. The entire volume of a crystal may be constructed by regular assembly of such blocks.

The term "space group" refers to the arrangement of symmetry elements of a crystal.

The term "molecular replacement" refers to a method that involves generating a preliminary model of a Pin1 crystal whose structure coordinates are not known, by orienting and positioning a molecule whose structure coordinates are known. Phases are then calculated from this model and combined with observed amplitudes to give an approximate Fourier synthesis of the structure whose coordinates are known.

The crystal structure coordinates of a Pin1 protein and its WW domain can be used to design compounds that bind to the protein and alter its physical or physiological properties in a variety of ways. The structure coordinates of the protein can also be used to computationally screen small molecule data bases for compounds that bind to the protein to develop competitive, uncompetitive and non-competitive inhibitors of Pin1 WW domain.

A "competitive" inhibitor is one that inhibits a WW domain activity (*e.g.*, a Pin1 WW domain activity) by binding to the same kinetic form, of the WW domain, as its substrate binds--thus directly competing with the substrate for the active site of

the WW domain. Competitive inhibition can be reversed completely by increasing the substrate concentration.

An "uncompetitive" inhibitor is one that inhibits WW domain activity (*e.g.*, a Pin1 WW domain activity) by binding to a different kinetic form of the active site than does the substrate. Such inhibitors bind to a WW domain already bound with the substrate and not to the free enzyme. Uncompetitive inhibition cannot be reversed completely by increasing the substrate concentration.

A "non-competitive" inhibitor is one that can bind to either the free or substrate bound form of a WW domain.

Those of skill in the art may identify inhibitors as competitive, uncompetitive or non-competitive, by computer fitting enzyme kinetic data using standard equations according to Segel, I. H., Enzyme Kinetics, J. Wiley & Sons, (1975). It should also be understood that uncompetitive or non-competitive inhibitors according to this invention may bind to an accessory binding site.

Methods of using crystal structure data to design inhibitors of enzyme activity are known in the art. Thus, the crystal structure data provided herein can be used in the design of new or improved enzymatic inhibitors. For example, the Pin1 WW domain coordinates, provided herein, can be superimposed onto other available coordinates of similar enzymes which have inhibitors bound to them to give an approximation of the way these and related inhibitors might bind to Pin1 WW domains. Alternatively, computer programs employed in the practice of rational drug design can be used to identify compounds that reproduce interaction characteristics similar to those found between the Pin1 WW domain and the co-crystalized substrate mimic. Furthermore, detailed knowledge of the nature of binding site interactions allows for the modification of compounds to alter or improve solubility, pharmacokinetics, *etc.* without affecting binding activity.

Computer programs are widely available that are capable of carrying out the activities necessary to design compounds using the crystal structure information

provided herein. Examples include, but are not limited to, the computer programs listed below:

Catalyst Databases™ - an information retrieval program accessing chemical databases such as BioByte Master File, Derwent WDI and ACD;

Catalyst/HYPO™ - generates models of compounds and hypotheses to explain variations of activity with the structure of drug candidates;

Ludi™ - fits molecules into the active site of a protein by identifying and matching complementary polar and hydrophobic groups;

Leapfrog™ - "grows" new ligands using an algorithm with parameters under the control of the user.

In addition, various general purpose machines may be used with programs written in accordance with the teachings herein, or it may be more convenient to construct more specialized apparatus to perform the operations. However, preferably the embodiment is implemented in one or more computer programs executing on programmable systems each comprising at least one processor, at least one data storage system (including volatile and non-volatile memory and/or storage elements), at least one input device, and at least one output device. The program is executed on the processor to perform the functions described herein.

Each such program may be implemented in any desired computer language (including machine, assembly, high level procedural, or object oriented programming languages) to communicate with a computer system. In any case, the language may be a compiled or interpreted language. The computer program will typically be stored on a storage media or device (*e.g.*, ROM, CD- ROM, or magnetic or optical media) readable by a general or special purpose programmable computer, for configuring and operating the computer when the storage media or device is read by the computer to perform the procedures described herein. The system may also be considered to be implemented as a computer-readable storage medium, configured with a computer program, where the

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storage medium so configured causes a computer to operate in a specific and predefined manner to perform the functions described herein.

Embodiments of the invention include systems (*e.g.*, internet based systems), particularly computer systems which store and manipulate the coordinate and sequence information described herein. One example of a computer system **100** is illustrated in block diagram form in Figure 5. As used herein, "a computer system" refers to the hardware components, software components, and data storage components used to analyze the coordinates and sequences set forth in Table 1. The computer system **100** typically includes a processor for processing, accessing and manipulating the sequence data. The processor **105** can be any well-known type of central processing unit, such as, for example, the Pentium III from Intel Corporation, or similar processor from Sun, Motorola, Compaq, AMD or International Business Machines.

Typically the computer system **100** is a general purpose system that comprises the processor **105** and one or more internal data storage components **110** for storing data, and one or more data retrieving devices for retrieving the data stored on the data storage components. A skilled artisan can readily appreciate that any one of the currently available computer systems are suitable.

In one particular embodiment, the computer system **100** includes a processor **105** connected to a bus which is connected to a main memory **115** (preferably implemented as RAM) and one or more internal data storage devices **110**, such as a hard drive and/or other computer readable media having data recorded thereon. In some embodiments, the computer system **100** further includes one or more data retrieving device **118** for reading the data stored on the internal data storage devices **110**.

The data retrieving device **118** may represent, for example, a floppy disk drive, a compact disk drive, a magnetic tape drive, or a modem capable of connection to a remote data storage system (*e.g.*, via the internet) etc. In some embodiments, the internal data storage device **110** is a removable computer readable medium such as a floppy disk, a compact disk, a magnetic tape, etc. containing control logic and/or data recorded thereon. The computer system **100** may advantageously include or be programmed by

appropriate software for reading the control logic and/or the data from the data storage component once inserted in the data retrieving device.

The computer system **100** includes a display **120** which is used to display output to a computer user. It should also be noted that the computer system **100** can be linked to other computer systems **125a-c** in a network or wide area network to provide centralized access to the computer system **100**.

Software for accessing and processing the coordinate and sequences of Table 1, (such as search tools, compare tools, and modeling tools etc.) may reside in main memory **115** during execution.

For the first time, the present invention permits the use of molecular design techniques to design, select and synthesize chemical entities and compounds, including inhibitory compounds, capable of binding to the active site or accessory binding site of a WW domain (e.g., a Pinl WW domain), in whole or in part.

One approach enabled by this invention, is to use the structure coordinates set forth in Table 1 to design compounds that bind to the enzyme and alter the physical properties of the compounds in different ways, *e.g.*, solubility. For example, this invention enables the design of compounds that act as competitive inhibitors of the WW domains by binding to, all or a portion of, the active site of a WW domain. This invention also enables the design of compounds that act as uncompetitive inhibitors of the WW domain (*e.g.*, the WW domain of Pin1). These inhibitors may bind to, all or a portion of, the active site of a WW domain. Similarly, non-competitive inhibitors that bind to and inhibit a WW domain whether or not it is bound to another chemical entity may be designed using the structure coordinates of the invention as set forth in Table 1.

In another approach a Pin1 WW domain crystal is probed with molecules composed of a variety of different chemical entities to determine optimal sites for interaction between candidate binding molecules (*e.g.*, inhibitors) and the WW domain active site.

In another embodiment, an approach made possible and enabled by this invention, is to screen computationally small molecule data bases for chemical entities or compounds that can bind in whole, or in part, to the WW domain. In this screening, the quality of fit of such entities or compounds to the binding site may be judged either by shape complementarity or by estimated interaction energy. Meng, E. C. *et al.*, J. Comp. Chem., 13, pp. 505-524 (1992).

A number of WW domains exist, many of which have similar functional activity. However, many WW domains may crystallize in more than one crystal form. Thus, the structure coordinates of Pin1 WW domain, or portions thereof, as provided by this invention are particularly useful to solve the structure of other crystal forms of WW domains. They may also be used to solve the structure of a WW domain or Pin1 WW domain mutants, WW domain co-complexes, or the crystalline form of any other protein with significant amino acid sequence homology to any WW domain.

One method that may be employed for this purpose is molecular replacement. In this method, the unknown crystal structure, whether it is another WW domain crystal form, a WW domain or Pin1 WW domain mutant, or a WW domain co-complex, or the crystal of some other protein with significant amino acid sequence homology to any WW domain, may be determined using the structure coordinates as provided in Table 1. This method will provide an accurate structural form for the unknown crystal more quickly and efficiently than attempting to determine such information *ab initio*. Those of skill in the art understand that a set of structure coordinates determined by X-ray crystallography is not without standard error.

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TABLE 1

Atom	Atom Type	Residue	#	X	Y	Z	OCC	B
1	C	GLY	1	.297	6.261	77.129	1.00	34.99
2	O	GLY	1	.701	5.443	77.948	1.00	35.67
3	N	GLY	1	-1.549	6.552	75.579	1.00	35.60
4	CA	GLY	1	-.294	5.819	75.824	1.00	35.38
5	N	SER	2	.327	7.566	77.321	1.00	34.27
6	CA	SER	2	.851	8.106	78.547	1.00	33.27
7	CB	SER	2	1.393	9.518	78.304	1.00	33.43
8	OG	SER	2	.397	10.429	77.856	1.00	34.33
9	C	SER	2	-.346	8.118	79.496	1.00	32.42
10	O	SER	2	-1.486	8.145	79.045	1.00	32.01
11	N	HIS	3	-.093	8.099	80.798	1.00	31.53
12	CA	HIS	3	-1.153	8.083	81.796	1.00	30.70
13	CB	HIS	3	-.530	8.274	83.186	1.00	30.18
14	CG	HIS	3	-1.523	8.316	84.304	1.00	29.99
15	CD2	HIS	3	-2.043	7.337	85.077	1.00	29.88
16	ND1	HIS	3	-2.102	9.493	84.732	1.00	29.83
17	CE1	HIS	3	-2.936	9.228	85.729	1.00	29.76
18	NE2	HIS	3	-2.915	7.930	85.954	1.00	29.65
19	C	HIS	3	-2.261	9.111	81.546	1.00	30.30
20	O	HIS	3	-3.428	8.818	81.767	1.00	30.00
21	N	GLY	4	-1.899	10.292	81.053	1.00	30.06
22	CA	GLY	4	-2.891	11.330	80.812	1.00	30.26
23	C	GLY	4	-3.491	11.392	79.417	1.00	30.62
24	O	GLY	4	-3.962	12.445	78.990	1.00	30.36
25	N	MET	5	-3.484	10.272	78.702	1.00	31.06
26	CA	MET	5	-4.029	10.239	77.349	1.00	32.14
27	CB	MET	5	-2.900	10.330	76.320	1.00	33.56
28	CG	MET	5	-1.877	11.379	76.665	1.00	35.79
29	SD	MET	5	-1.479	12.502	75.352	1.00	39.48
30	CE	MET	5	-2.891	13.512	75.389	1.00	38.05
31	C	MET	5	-4.816	8.967	77.107	1.00	32.01
32	O	MET	5	-4.592	7.954	77.770	1.00	31.57
33	N	ALA	6	-5.743	9.024	76.156	1.00	32.09
34	CA	ALA	6	-6.544	7.858	75.823	1.00	32.75
35	CB	ALA	6	-7.620	8.224	74.808	1.00	32.26
36	C	ALA	6	-5.593	6.840	75.226	1.00	33.51
37	O	ALA	6	-4.579	7.208	74.625	1.00	32.76
38	N	ASP	7	-5.900	5.561	75.408	1.00	34.83
39	CA	ASP	7	-5.050	4.523	74.847	1.00	36.77
40	CB	ASP	7	-5.191	3.201	75.574	1.00	36.60
41	CG	ASP	7	-4.345	3.133	76.794	1.00	36.46
42	OD1	ASP	7	-3.300	3.815	76.824	1.00	36.44
43	OD2	ASP	7	-4.722	2.392	77.717	1.00	36.77
44	C	ASP	7	-5.426	4.277	73.431	1.00	38.24
45	O	ASP	7	-6.399	4.833	72.926	1.00	38.39
46	N	GLU	8	-4.675	3.410	72.778	1.00	39.91
47	CA	GLU	8	-5.037	3.176	71.420	1.00	41.61
48	CB	GLU	8	-5.005	4.516	70.665	1.00	42.47
49	CG	GLU	8	-3.630	5.196	70.661	1.00	43.94
50	CD	GLU	8	-3.700	6.679	70.399	1.00	44.72
51	OE1	GLU	8	-3.249	7.133	69.317	1.00	45.25

52	OE2	GLU	8	-4.209	7.410	71.267	1.00	45.66
53	C	GLU	8	-4.350	2.129	70.591	1.00	42.09
54	O	GLU	8	-3.395	1.444	70.989	1.00	42.27
55	N	GLU	9	-4.940	2.032	69.418	1.00	42.95
56	CA	GLU	9	-4.606	1.219	68.258	1.00	43.60
57	CB	GLU	9	-3.972	2.124	67.200	1.00	44.31
58	CG	GLU	9	-3.671	3.542	67.569	1.00	45.81
59	CD	GLU	9	-4.496	4.518	66.738	1.00	46.50
60	OE1	GLU	9	-5.535	4.977	67.255	1.00	47.27
61	OE2	GLU	9	-4.138	4.816	65.573	1.00	47.08
62	C	GLU	9	-3.933	-.102	68.005	1.00	43.44
63	O	GLU	9	-3.420	-.838	68.845	1.00	43.85
64	N	LYS	10	-3.912	-.276	66.690	1.00	43.38
65	CA	LYS	10	-3.326	-1.359	65.963	1.00	42.60
66	CB	LYS	10	-4.363	-2.078	65.091	1.00	43.20
67	CG	LYS	10	-5.105	-3.248	65.688	1.00	43.83
68	CD	LYS	10	-6.580	-2.891	65.718	1.00	44.18
69	CE	LYS	10	-7.473	-3.925	65.065	1.00	44.53
70	NZ	LYS	10	-8.832	-3.339	64.817	1.00	44.81
71	C	LYS	10	-2.521	-.539	64.995	1.00	41.77
72	O	LYS	10	-1.396	-.087	65.248	1.00	41.98
73	N	LEU	11	-3.210	-.290	63.894	1.00	40.35
74	CA	LEU	11	-2.678	.402	62.758	1.00	38.97
75	CG	LEU	11	-2.843	2.889	63.092	1.00	38.96
76	CD1	LEU	11	-4.128	2.512	63.814	1.00	38.82
77	CD2	LEU	11	-2.222	4.141	63.685	1.00	38.60
78	C	LEU	11	-1.778	-.681	62.212	1.00	37.68
79	O	LEU	11	-.725	-.986	62.778	1.00	37.95
80	CB	LEU	11	-1.911	1.672	63.158	1.00	38.94
81	N	PRO	12	-2.216	-1.315	61.126	1.00	36.04
82	CD	PRO	12	-3.360	-.954	60.273	1.00	35.90
83	CA	PRO	12	-1.421	-2.381	60.519	1.00	34.36
84	CB	PRO	12	-2.183	-2.692	59.236	1.00	34.88
85	CG	PRO	12	-3.597	-2.239	59.553	1.00	35.30
86	C	PRO	12	-.049	-1.801	60.240	1.00	32.67
87	O	PRO	12	.151	-.586	60.330	1.00	32.19
88	N	PRO	13	.929	-2.652	59.924	1.00	31.08
89	CD	PRO	13	.963	-4.125	59.872	1.00	30.89
90	CA	PRO	13	2.248	-2.084	59.654	1.00	29.59
91	CB	PRO	13	3.042	-3.293	59.165	1.00	30.16
92	CG	PRO	13	2.438	-4.419	59.971	1.00	30.57
93	C	PRO	13	2.140	-.985	58.593	1.00	28.22
94	O	PRO	13	1.302	-1.062	57.689	1.00	27.79
95	N	GLY	14	2.966	.047	58.737	1.00	26.74
96	CA	GLY	14	2.970	1.140	57.783	1.00	25.25
97	C	GLY	14	2.066	2.317	58.092	1.00	24.24
98	O	GLY	14	2.264	3.403	57.553	1.00	23.92
99	N	TRP	15	1.081	2.124	58.960	1.00	23.51
100	CA	TRP	15	.160	3.205	59.286	1.00	22.91
101	CB	TRP	15	-1.275	2.679	59.368	1.00	22.23
102	CG	TRP	15	-1.845	2.209	58.065	1.00	21.67
103	CD2	TRP	15	-2.524	3.010	57.092	1.00	21.24
104	CE2	TRP	15	-2.898	2.152	56.032	1.00	21.30
105	CE3	TRP	15	-2.853	4.371	57.011	1.00	20.98
106	CD1	TRP	15	-1.832	.935	57.573	1.00	21.71
107	NE1	TRP	15	-2.462	.893	56.352	1.00	21.40

108	CZ2	TRP	15	-3.588	2.609	54.902	1.00	21.06
109	CZ3	TRP	15	-3.540	4.829	55.884	1.00	21.18
110	CH2	TRP	15	-3.898	3.946	54.845	1.00	21.04
111	C	TRP	15	.470	3.954	60.575	1.00	23.13
112	O	TRP	15	1.032	3.402	61.519	1.00	22.54
113	N	GLU	16	.085	5.223	60.596	1.00	23.37
114	CA	GLU	16	.267	6.065	61.763	1.00	24.62
115	CB	GLU	16	1.619	6.790	61.698	1.00	24.57
116	CG	GLU	16	1.788	7.743	60.532	1.00	24.62
117	CD	GLU	16	3.200	8.311	60.448	1.00	24.61
118	OE1	GLU	16	4.114	7.598	59.988	1.00	24.24
119	OE2	GLU	16	3.395	9.470	60.857	1.00	24.99
120	C	GLU	16	-.890	7.063	61.812	1.00	25.27
121	O	GLU	16	-1.487	7.384	60.784	1.00	24.68
122	N	LYS	17	-1.224	7.526	63.012	1.00	26.55
123	CA	LYS	17	-2.307	8.486	63.173	1.00	28.35
124	CB	LYS	17	-3.042	8.285	64.502	1.00	29.42
125	CG	LYS	17	-4.042	9.410	64.769	1.00	31.85
126	CD	LYS	17	-4.548	9.476	66.204	1.00	33.36
127	CE	LYS	17	-5.308	8.228	66.599	1.00	34.45
128	NZ	LYS	17	-4.377	7.166	67.041	1.00	36.19
129	C	LYS	17	-1.781	9.910	63.142	1.00	29.19
130	O	LYS	17	-.680	10.188	63.617	1.00	28.99
131	N	ARG	18	-2.577	10.818	62.593	1.00	30.37
132	CA	ARG	18	-2.184	12.215	62.536	1.00	31.87
133	CB	ARG	18	-1.435	12.482	61.233	1.00	32.64
134	CG	ARG	18	-.238	11.563	61.069	1.00	34.24
135	CD	ARG	18	.498	11.835	59.791	1.00	35.78
136	NE	ARG	18	1.196	13.109	59.859	1.00	37.48
137	CZ	ARG	18	2.517	13.230	59.884	1.00	37.91
138	NH1	ARG	18	3.066	14.428	59.952	1.00	38.43
139	NH2	ARG	18	3.291	12.154	59.830	1.00	38.32
140	C	ARG	18	-3.394	13.127	62.672	1.00	32.46
141	O	ARG	18	-4.531	12.658	62.697	1.00	32.20
142	N	MET	19	-3.146	14.428	62.777	1.00	33.73
143	CA	MET	19	-4.224	15.396	62.922	1.00	35.12
144	CB	MET	19	-4.089	16.168	64.236	1.00	36.75
145	CG	MET	19	-4.642	15.457	65.452	1.00	39.07
146	SD	MET	19	-5.206	16.611	66.735	1.00	41.46
147	CE	MET	19	-5.153	18.203	65.865	1.00	41.00
148	C	MET	19	-4.293	16.405	61.790	1.00	35.20
149	O	MET	19	-3.269	16.886	61.306	1.00	35.22
150	N	SER	20	-5.514	16.727	61.381	1.00	35.36
151	CA	SER	20	-5.740	17.705	60.328	1.00	35.66
152	CB	SER	20	-7.184	17.609	59.825	1.00	35.65
153	OG	SER	20	-7.675	18.875	59.414	1.00	35.43
154	C	SER	20	-5.480	19.098	60.891	1.00	36.12
155	O	SER	20	-6.091	19.496	61.883	1.00	35.85
156	N	ARG	21	-4.557	19.828	60.272	1.00	36.76
157	CA	ARG	21	-4.238	21.186	60.711	1.00	37.41
158	CB	ARG	21	-3.125	21.796	59.844	1.00	38.05
159	CG	ARG	21	-1.694	21.415	60.217	1.00	39.57
160	CD	ARG	21	-1.064	20.438	59.224	1.00	41.03
161	NE	ARG	21	-1.805	20.360	57.971	1.00	42.01
162	CZ	ARG	21	-1.230	20.319	56.770	1.00	42.70
163	NH1	ARG	21	.094	20.355	56.660	1.00	43.34

164	NH2	ARG	21	-1.972	20.225	55.672	1.00	43.27
165	C	ARG	21	-5.488	22.053	60.579	1.00	37.21
166	O	ARG	21	-5.701	22.983	61.354	1.00	37.49
167	N	SER	22	-6.311	21.729	59.589	1.00	36.91
168	CA	SER	22	-7.527	22.473	59.303	1.00	36.54
169	CB	SER	22	-7.950	22.201	57.856	1.00	37.25
170	OG	SER	22	-9.308	22.541	57.643	1.00	37.97
171	C	SER	22	-8.726	22.265	60.227	1.00	35.96
172	O	SER	22	-9.326	23.235	60.690	1.00	36.13
173	N	SER	23	-9.076	21.012	60.496	1.00	34.79
174	CA	SER	23	-10.240	20.720	61.330	1.00	33.65
175	CB	SER	23	-11.163	19.756	60.584	1.00	33.79
176	OG	SER	23	-10.514	18.517	60.357	1.00	34.00
177	C	SER	23	-9.957	20.148	62.715	1.00	32.65
178	O	SER	23	-10.855	20.100	63.558	1.00	32.30
179	N	GLY	24	-8.723	19.716	62.951	1.00	31.54
180	CA	GLY	24	-8.383	19.130	64.236	1.00	30.56
181	C	GLY	24	-8.857	17.686	64.277	1.00	29.75
182	O	GLY	24	-8.703	16.981	65.276	1.00	29.78
183	N	ARG	25	-9.445	17.251	63.169	1.00	28.87
184	CA	ARG	25	-9.963	15.896	63.019	1.00	28.00
185	CB	ARG	25	-10.936	15.884	61.838	1.00	29.15
186	CG	ARG	25	-11.631	14.576	61.522	1.00	30.49
187	CD	ARG	25	-12.548	14.810	60.330	1.00	31.64
188	NE	ARG	25	-13.153	13.592	59.806	1.00	32.91
189	CZ	ARG	25	-13.796	13.531	58.645	1.00	32.93
190	NH1	ARG	25	-13.913	14.617	57.892	1.00	33.35
191	NH2	ARG	25	-14.316	12.384	58.232	1.00	33.50
192	C	ARG	25	-8.806	14.916	62.783	1.00	27.17
193	O	ARG	25	-7.846	15.235	62.081	1.00	26.80
194	N	VAL	26	-8.894	13.732	63.380	1.00	25.90
195	CA	VAL	26	-7.851	12.717	63.223	1.00	25.40
196	CB	VAL	26	-7.943	11.640	64.341	1.00	25.46
197	CG1	VAL	26	-7.058	10.451	64.006	1.00	25.92
198	CG2	VAL	26	-7.524	12.233	65.675	1.00	25.82
199	C	VAL	26	-7.960	12.007	61.877	1.00	24.87
200	O	VAL	26	-9.054	11.824	61.353	1.00	25.20
201	N	TYR	27	-6.819	11.621	61.313	1.00	24.40
202	CA	TYR	27	-6.803	10.886	60.051	1.00	23.42
203	CG	TYR	27	-5.442	12.563	58.582	1.00	24.14
204	CD1	TYR	27	-4.434	11.985	57.803	1.00	24.61
205	CE1	TYR	27	-3.266	12.688	57.496	1.00	24.81
206	CD2	TYR	27	-5.245	13.858	59.055	1.00	24.39
207	CE2	TYR	27	-4.084	14.567	58.758	1.00	25.05
208	CZ	TYR	27	-3.100	13.981	57.978	1.00	25.21
209	OH	TYR	27	-1.962	14.698	57.683	1.00	25.76
210	C	TYR	27	-5.624	9.925	60.069	1.00	23.02
211	O	TYR	27	-4.774	9.999	60.960	1.00	22.89
212	CB	TYR	27	-6.746	11.836	58.839	1.00	23.85
213	N	TYR	28	-5.575	9.014	59.103	1.00	21.88
214	CA	TYR	28	-4.504	8.034	59.074	1.00	21.16
215	CB	TYR	28	-5.095	6.632	59.223	1.00	22.27
216	CG	TYR	28	-5.914	6.520	60.488	1.00	23.24
217	CD1	TYR	28	-7.210	7.032	60.550	1.00	24.01
218	CE1	TYR	28	-7.926	7.036	61.745	1.00	24.83
219	CD2	TYR	28	-5.358	5.997	61.652	1.00	23.92

220	CE2	TYR	28	-6.062	5.996	62.852	1.00	24.76
221	CZ	TYR	28	-7.343	6.519	62.891	1.00	25.17
222	OH	TYR	28	-8.019	6.553	64.087	1.00	26.30
223	C	TYR	28	-3.632	8.138	57.837	1.00	20.21
224	O	TYR	28	-4.118	8.323	56.725	1.00	19.01
225	N	PHE	29	-2.332	8.017	58.065	1.00	19.58
226	CA	PHE	29	-1.327	8.134	57.024	1.00	18.83
227	CB	PHE	29	-.461	9.359	57.344	1.00	19.22
228	CG	PHE	29	.776	9.488	56.506	1.00	19.30
229	CD1	PHE	29	.691	9.778	55.149	1.00	19.41
230	CD2	PHE	29	2.034	9.366	57.089	1.00	19.57
231	CE1	PHE	29	1.843	9.952	54.386	1.00	19.63
232	CE2	PHE	29	3.191	9.538	56.337	1.00	19.77
233	CZ	PHE	29	3.098	9.831	54.984	1.00	19.44
234	C	PHE	29	-.468	6.878	56.936	1.00	18.34
235	O	PHE	29	-.029	6.337	57.951	1.00	18.15
236	N	ASN	30	-.241	6.407	55.716	1.00	17.82
237	CA	ASN	30	.595	5.232	55.513	1.00	17.50
238	CB	ASN	30	-.032	4.307	54.464	1.00	17.63
239	CG	ASN	30	.741	3.019	54.287	1.00	17.60
240	OD1	ASN	30	1.913	3.032	53.908	1.00	17.34
241	ND2	ASN	30	.088	1.893	54.563	1.00	18.35
242	C	ASN	30	1.928	5.781	55.017	1.00	17.59
243	O	ASN	30	1.975	6.414	53.963	1.00	16.77
244	N	HIS	31	3.003	5.557	55.774	1.00	17.16
245	CA	HIS	31	4.306	6.075	55.377	1.00	17.86
246	CB	HIS	31	5.202	6.312	56.607	1.00	18.00
247	CG	HIS	31	5.404	5.105	57.470	1.00	18.54
248	CD2	HIS	31	6.042	3.934	57.234	1.00	18.99
249	ND1	HIS	31	4.955	5.041	58.772	1.00	18.72
250	CE1	HIS	31	5.310	3.883	59.301	1.00	19.47
251	NE2	HIS	31	5.971	3.193	58.388	1.00	18.96
252	C	HIS	31	5.052	5.259	54.328	1.00	17.93
253	O	HIS	31	6.205	5.554	54.019	1.00	18.12
254	N	ILE	32	4.396	4.243	53.773	1.00	17.83
255	CA	ILE	32	5.006	3.425	52.729	1.00	17.67
256	CB	ILE	32	4.772	1.909	52.968	1.00	18.12
257	CG2	ILE	32	5.434	1.097	51.854	1.00	17.77
258	CG1	ILE	32	5.357	1.492	54.321	1.00	18.34
259	CD1	ILE	32	5.138	.027	54.656	1.00	19.67
260	C	ILE	32	4.382	3.823	51.387	1.00	17.44
261	O	ILE	32	5.078	3.950	50.379	1.00	17.36
262	N	THR	33	3.067	4.035	51.385	1.00	17.20
263	CA	THR	33	2.348	4.425	50.170	1.00	17.33
264	CB	THR	33	.955	3.775	50.109	1.00	17.42
265	OG1	THR	33	.134	4.338	51.141	1.00	17.75
266	CG2	THR	33	1.050	2.271	50.319	1.00	18.24
267	C	THR	33	2.131	5.939	50.135	1.00	17.18
268	O	THR	33	1.838	6.512	49.085	1.00	16.30
269	N	ASN	34	2.270	6.568	51.299	1.00	17.25
270	CA	ASN	34	2.075	8.002	51.467	1.00	17.74
271	CB	ASN	34	3.024	8.795	50.559	1.00	18.75
272	CG	ASN	34	4.464	8.737	51.047	1.00	20.18
273	OD1	ASN	34	4.712	8.518	52.236	1.00	21.35
274	ND2	ASN	34	5.416	8.947	50.144	1.00	20.59
275	C	ASN	34	.629	8.443	51.262	1.00	17.42

276	O	ASN	34	.347	9.621	51.034	1.00	17.41
277	N	ALA	35	-.291	7.491	51.371	1.00	17.84
278	CA	ALA	35	-1.711	7.792	51.224	1.00	18.28
279	CB	ALA	35	-2.458	6.563	50.741	1.00	18.12
280	C	ALA	35	-2.300	8.262	52.553	1.00	19.15
281	O	ALA	35	-1.847	7.848	53.620	1.00	18.60
282	N	SER	36	-3.309	9.129	52.472	1.00	19.81
283	CA	SER	36	-3.999	9.651	53.650	1.00	21.25
284	CB	SER	36	-3.828	11.172	53.752	1.00	21.07
285	OG	SER	36	-2.486	11.530	54.036	1.00	22.28
286	C	SER	36	-5.487	9.325	53.541	1.00	22.07
287	O	SER	36	-6.075	9.447	52.469	1.00	21.66
288	N	GLN	37	-6.091	8.910	54.650	1.00	23.28
289	CA	GLN	37	-7.516	8.586	54.669	1.00	24.65
290	CB	GLN	37	-7.739	7.112	54.317	1.00	24.61
291	CG	GLN	37	-7.084	6.119	55.269	1.00	24.96
292	CD	GLN	37	-7.343	4.676	54.868	1.00	25.43
293	OE1	GLN	37	-7.116	4.289	53.724	1.00	25.92
294	NE2	GLN	37	-7.814	3.872	55.814	1.00	26.05
295	C	GLN	37	-8.104	8.881	56.047	1.00	25.98
296	O	GLN	37	-7.414	8.775	57.058	1.00	25.84
297	N	TRP	38	-9.381	9.252	56.076	1.00	27.72
298	CA	TRP	38	-10.074	9.568	57.322	1.00	29.72
299	CB	TRP	38	-11.405	10.268	57.024	1.00	29.29
300	CG	TRP	38	-11.277	11.647	56.461	1.00	29.14
301	CD2	TRP	38	-10.665	12.776	57.092	1.00	28.85
302	CE2	TRP	38	-10.802	13.872	56.209	1.00	28.94
303	CE3	TRP	38	-10.012	12.977	58.316	1.00	29.21
304	CD1	TRP	38	-11.745	12.085	55.257	1.00	29.21
305	NE1	TRP	38	-11.466	13.421	55.097	1.00	29.11
306	CZ2	TRP	38	-10.310	15.145	56.509	1.00	28.81
307	CZ3	TRP	38	-9.521	14.244	58.618	1.00	28.69
308	CH2	TRP	38	-9.675	15.312	57.715	1.00	28.99
309	C	TRP	38	-10.362	8.336	58.173	1.00	31.49
310	O	TRP	38	-10.200	8.354	59.392	1.00	31.14
311	N	GLU	39	-10.801	7.270	57.518	1.00	33.88
312	CA	GLU	39	-11.150	6.033	58.195	1.00	36.66
313	CB	GLU	39	-11.931	5.142	57.226	1.00	37.87
314	CG	GLU	39	-11.732	3.645	57.392	1.00	40.11
315	CD	GLU	39	-10.922	3.045	56.255	1.00	41.50
316	OE1	GLU	39	-10.937	1.802	56.096	1.00	42.21
317	OE2	GLU	39	-10.267	3.818	55.521	1.00	42.41
318	C	GLU	39	-9.960	5.283	58.764	1.00	37.86
319	O	GLU	39	-8.928	5.133	58.104	1.00	37.68
320	N	ARG	40	-10.097	4.821	60.002	1.00	39.22
321	CA	ARG	40	-9.016	4.066	60.600	1.00	41.26
322	CB	ARG	40	-9.346	3.634	62.027	1.00	41.97
323	CG	ARG	40	-8.215	2.858	62.681	1.00	43.45
324	CD	ARG	40	-8.414	2.794	64.176	1.00	44.68
325	NE	ARG	40	-9.631	2.070	64.530	1.00	46.28
326	CZ	ARG	40	-10.399	2.374	65.571	1.00	47.26
327	NH1	ARG	40	-10.079	3.399	66.349	1.00	47.90
328	NH2	ARG	40	-11.465	1.635	65.863	1.00	47.94
329	C	ARG	40	-8.889	2.847	59.709	1.00	42.22
330	O	ARG	40	-9.829	2.067	59.568	1.00	42.01
331	N	PRO	41	-7.728	2.679	59.073	1.00	43.30

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332	CD	PRO	41	-6.426	3.285	59.408	1.00	43.24
333	CA	PRO	41	-7.557	1.519	58.200	1.00	44.44
334	CB	PRO	41	-6.118	1.664	57.735	1.00	43.99
335	CG	PRO	41	-5.452	2.215	58.973	1.00	43.52
336	C	PRO	41	-7.747	.295	59.076	1.00	45.67
337	O	PRO	41	-8.151	-.769	58.614	1.00	45.96
338	N	SER	42	-7.472	.509	60.359	1.00	47.15
339	CA	SER	42	-7.526	-.488	61.419	1.00	48.41
340	CB	SER	42	-8.015	-1.848	60.914	1.00	48.76
341	OG	SER	42	-7.942	-2.822	61.941	1.00	49.21
342	C	SER	42	-6.080	-.596	61.874	1.00	48.94
343	O	SER	42	-5.460	.476	62.034	1.00	49.50
344	OT	SER	42	-5.583	-1.728	62.054	1.00	49.73
345	CB	GLU	55	3.104	-8.396	51.102	1.00	46.42
346	CG	GLU	55	4.292	-9.110	50.504	1.00	47.06
347	CD	GLU	55	5.366	-8.171	50.026	1.00	47.19
348	OE1	GLU	55	6.311	-8.655	49.370	1.00	47.56
349	OE2	GLU	55	5.270	-6.959	50.306	1.00	47.58
350	C	GLU	55	1.824	-10.384	50.300	1.00	45.13
351	O	GLU	55	2.186	-11.549	50.483	1.00	45.49
352	N	GLU	55	2.230	-10.050	52.720	1.00	46.15
353	CA	GLU	55	1.954	-9.349	51.424	1.00	45.81
354	N	PRO	56	1.293	-9.977	49.133	1.00	44.26
355	CD	PRO	56	.521	-8.734	48.948	1.00	44.19
356	CA	PRO	56	1.121	-10.878	47.985	1.00	43.03
357	CB	PRO	56	-.036	-10.239	47.221	1.00	43.46
358	CG	PRO	56	.152	-8.781	47.476	1.00	44.13
359	C	PRO	56	2.383	-11.033	47.128	1.00	41.84
360	O	PRO	56	3.294	-10.210	47.218	1.00	41.90
361	N	ALA	57	2.432	-12.076	46.295	1.00	40.21
362	CA	ALA	57	3.609	-12.319	45.462	1.00	38.35
363	CB	ALA	57	3.696	-13.780	45.098	1.00	38.82
364	C	ALA	57	3.717	-11.470	44.202	1.00	36.94
365	O	ALA	57	4.824	-11.120	43.791	1.00	36.85
366	N	ARG	58	2.590	-11.163	43.568	1.00	34.78
367	CA	ARG	58	2.612	-10.324	42.363	1.00	32.26
368	CB	ARG	58	2.433	-11.170	41.088	1.00	33.84
369	CG	ARG	58	.964	-11.340	40.690	1.00	35.66
370	CD	ARG	58	.702	-12.385	39.614	1.00	37.32
371	NE	ARG	58	1.340	-12.096	38.335	1.00	38.74
372	CZ	ARG	58	.736	-12.218	37.156	1.00	39.29
373	NH1	ARG	58	-.530	-12.610	37.085	1.00	40.23
374	NH2	ARG	58	1.412	-11.984	36.045	1.00	39.66
375	C	ARG	58	1.473	-9.306	42.441	1.00	29.53
376	O	ARG	58	.411	-9.579	43.005	1.00	29.35
377	N	VAL	59	1.712	-8.120	41.904	1.00	26.26
378	CA	VAL	59	.684	-7.095	41.881	1.00	23.07
379	CB	VAL	59	.893	-6.012	42.976	1.00	22.71
380	CG1	VAL	59	.819	-6.639	44.359	1.00	22.02
381	CG2	VAL	59	2.230	-5.310	42.773	1.00	21.89
382	C	VAL	59	.724	-6.417	40.518	1.00	21.53
383	O	VAL	59	1.769	-6.389	39.867	1.00	21.30
384	N	ARG	60	-.416	-5.912	40.062	1.00	19.57
385	CA	ARG	60	-.450	-5.188	38.796	1.00	18.00
386	CB	ARG	60	-1.483	-5.779	37.823	1.00	18.09

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387	CG	ARG	60	-1.471	-5.086	36.447	1.00	17.67
388	CD	ARG	60	-2.256	-5.867	35.402	1.00	18.99
389	NE	ARG	60	-2.107	-5.292	34.067	1.00	18.15
390	CZ	ARG	60	-2.522	-5.880	32.949	1.00	19.10
391	NH1	ARG	60	-3.115	-7.068	33.004	1.00	19.83
392	NH2	ARG	60	-2.345	-5.286	31.776	1.00	18.46
393	C	ARG	60	-.820	-3.749	39.146	1.00	17.26
394	O	ARG	60	-1.755	-3.515	39.911	1.00	16.91
395	N	CYS	61	-.077	-2.791	38.599	1.00	16.03
396	CA	CYS	61	-.332	-1.383	38.885	1.00	15.56
397	CB	CYS	61	.703	-.832	39.874	1.00	15.78
398	SG	CYS	61	.737	-1.592	41.504	1.00	16.00
399	C	CYS	61	-.283	-.503	37.653	1.00	15.27
400	O	CYS	61	.294	-.866	36.626	1.00	15.20
401	N	SER	62	-.912	.659	37.783	1.00	14.94
402	CA	SER	62	-.921	1.687	36.758	1.00	14.50
403	CB	SER	62	-2.350	2.013	36.295	1.00	14.59
404	OG	SER	62	-2.926	.951	35.554	1.00	15.92
405	C	SER	62	-.357	2.876	37.528	1.00	14.32
406	O	SER	62	-.457	2.918	38.756	1.00	14.45
407	N	HIS	63	.255	3.828	36.837	1.00	14.07
408	CA	HIS	63	.775	4.997	37.534	1.00	13.79
409	CB	HIS	63	2.214	4.767	38.050	1.00	13.87
410	CG	HIS	63	3.268	4.841	36.986	1.00	12.81
411	CD2	HIS	63	3.254	4.470	35.683	1.00	12.77
412	ND1	HIS	63	4.535	5.332	37.229	1.00	12.86
413	CE1	HIS	63	5.253	5.261	36.121	1.00	12.48
414	NE2	HIS	63	4.498	4.741	35.169	1.00	12.51
415	C	HIS	63	.755	6.231	36.656	1.00	14.12
416	O	HIS	63	.527	6.155	35.442	1.00	13.58
417	N	LEU	64	.975	7.371	37.300	1.00	13.67
418	CA	LEU	64	1.039	8.657	36.629	1.00	14.24
419	CB	LEU	64	-.157	9.534	37.017	1.00	14.20
420	CG	LEU	64	-.348	10.859	36.269	1.00	13.73
421	CD1	LEU	64	-1.743	11.410	36.579	1.00	13.74
422	CD2	LEU	64	.728	11.857	36.672	1.00	13.72
423	C	LEU	64	2.332	9.262	37.148	1.00	14.32
424	O	LEU	64	2.483	9.500	38.348	1.00	14.19
425	N	LEU	65	3.274	9.477	36.241	1.00	14.06
426	CA	LEU	65	4.565	10.035	36.599	1.00	14.02
427	CB	LEU	65	5.679	9.243	35.903	1.00	14.26
428	CG	LEU	65	7.092	9.842	35.944	1.00	14.74
429	CD1	LEU	65	7.665	9.719	37.343	1.00	14.55
430	CD2	LEU	65	7.985	9.116	34.937	1.00	15.55
431	C	LEU	65	4.691	11.501	36.206	1.00	13.95
432	O	LEU	65	4.282	11.897	35.116	1.00	14.13
433	N	VAL	66	5.249	12.301	37.108	1.00	14.28
434	CA	VAL	66	5.505	13.705	36.821	1.00	14.89
435	CB	VAL	66	4.722	14.663	37.732	1.00	14.74
436	CG1	VAL	66	5.136	16.114	37.436	1.00	14.38
437	CG2	VAL	66	3.226	14.508	37.474	1.00	14.30
438	C	VAL	66	6.998	13.896	37.056	1.00	15.76
439	O	VAL	66	7.478	13.799	38.181	1.00	15.04
440	N	LYS	67	7.728	14.141	35.977	1.00	17.10
441	CA	LYS	67	9.170	14.323	36.060	1.00	19.07
442	CB	LYS	67	9.816	14.024	34.704	1.00	19.17

443	CG	LYS	67	9.681	12.576	34.249	1.00	19.96
444	CD	LYS	67	10.220	12.400	32.831	1.00	21.24
445	CE	LYS	67	10.079	10.963	32.351	1.00	22.22
446	NZ	LYS	67	10.514	10.819	30.931	1.00	23.59
447	C	LYS	67	9.554	15.722	36.486	1.00	20.36
448	O	LYS	67	8.754	16.657	36.427	1.00	19.61
449	N	HIS	68	10.788	15.852	36.944	1.00	22.14
450	CA	HIS	68	11.305	17.150	37.326	1.00	24.68
451	CB	HIS	68	10.959	17.500	38.781	1.00	23.82
452	CG	HIS	68	11.279	16.418	39.767	1.00	23.00
453	CD2	HIS	68	10.535	15.376	40.206	1.00	22.29
454	ND1	HIS	68	12.474	16.353	40.457	1.00	22.27
455	CE1	HIS	68	12.447	15.317	41.279	1.00	22.06
456	NE2	HIS	68	11.282	14.709	41.144	1.00	22.01
457	C	HIS	68	12.791	17.131	37.163	1.00	27.35
458	O	HIS	68	13.433	16.081	37.148	1.00	27.13
459	N	SER	69	13.355	18.308	36.994	1.00	30.89
460	CA	SER	69	14.775	18.308	36.897	1.00	34.40
461	CB	SER	69	15.244	18.838	35.543	1.00	34.61
462	OG	SER	69	15.706	20.178	35.621	1.00	35.84
463	C	SER	69	15.293	19.163	37.995	1.00	36.47
464	O	SER	69	14.590	19.957	38.598	1.00	37.00
465	N	GLN	70	16.583	18.973	38.223	1.00	38.95
466	CA	GLN	70	17.367	19.695	39.189	1.00	41.20
467	CB	GLN	70	17.492	18.890	40.487	1.00	41.86
468	CG	GLN	70	16.693	19.525	41.612	1.00	42.77
469	CD	GLN	70	15.738	20.580	41.084	1.00	43.51
470	OE1	GLN	70	14.551	20.313	40.872	1.00	43.82
471	NE2	GLN	70	16.262	21.783	40.840	1.00	43.80
472	C	GLN	70	18.677	19.796	38.428	1.00	42.52
473	O	GLN	70	19.652	20.399	38.907	1.00	42.72
474	N	SER	71	18.716	19.253	37.209	1.00	43.97
475	CA	SER	71	19.912	19.354	36.382	1.00	45.24
476	CB	SER	71	19.702	18.674	35.001	1.00	45.44
477	OG	SER	71	20.900	18.043	34.546	1.00	45.95
478	C	SER	71	20.205	20.854	36.231	1.00	46.00
479	O	SER	71	19.398	21.716	36.627	1.00	46.32
480	N	ARG	72	21.399	21.159	35.725	1.00	46.57
481	CA	ARG	72	21.850	22.537	35.500	1.00	46.94
482	CB	ARG	72	22.259	23.216	36.794	1.00	48.06
483	CG	ARG	72	21.684	22.526	38.005	1.00	49.63
484	CD	ARG	72	21.477	23.518	39.070	1.00	50.70
485	NE	ARG	72	20.485	23.091	40.041	1.00	51.89
486	CZ	ARG	72	20.430	23.601	41.262	1.00	52.35
487	NH1	ARG	72	21.324	24.520	41.595	1.00	52.65
488	NH2	ARG	72	19.489	23.230	42.128	1.00	52.66
489	C	ARG	72	23.062	22.479	34.601	1.00	46.51
490	O	ARG	72	24.184	22.798	35.024	1.00	46.64
491	N	ARG	73	22.814	22.081	33.360	1.00	45.96
492	CA	ARG	73	23.879	21.899	32.398	1.00	45.39
493	CG	ARG	73	24.151	19.544	31.589	1.00	47.17
494	CD	ARG	73	23.266	18.375	31.298	1.00	47.97
495	NE	ARG	73	23.914	17.121	31.650	1.00	48.93
496	CZ	ARG	73	23.247	16.008	31.924	1.00	49.41
497	NH1	ARG	73	21.919	16.010	31.889	1.00	49.70
498	NH2	ARG	73	23.903	14.894	32.224	1.00	49.54

499	C	ARG	73	24.299	23.187	31.764	1.00	44.29
500	O	ARG	73	23.573	24.172	31.815	1.00	44.19
501	CB	ARG	73	23.446	20.862	31.347	1.00	46.07
502	N	PRO	74	25.508	23.194	31.207	1.00	43.29
503	CD	PRO	74	26.463	22.081	31.312	1.00	43.00
504	CA	PRO	74	26.121	24.335	30.542	1.00	42.23
505	CB	PRO	74	27.530	23.825	30.237	1.00	42.68
506	CG	PRO	74	27.756	22.815	31.345	1.00	43.08
507	C	PRO	74	25.365	24.817	29.312	1.00	41.42
508	O	PRO	74	24.605	24.071	28.686	1.00	40.74
509	N	SER	75	25.596	26.086	28.995	1.00	40.30
510	CA	SER	75	24.978	26.779	27.871	1.00	39.65
511	CB	SER	75	25.718	28.096	27.652	1.00	39.45
512	OG	SER	75	27.103	27.849	27.475	1.00	38.69
513	C	SER	75	24.919	26.030	26.542	1.00	39.09
514	O	SER	75	23.947	26.156	25.800	1.00	39.22
515	N	SER	76	25.964	25.268	26.243	1.00	38.45
516	CA	SER	76	26.042	24.536	24.983	1.00	37.90
517	CB	SER	76	27.432	23.907	24.838	1.00	37.86
518	OG	SER	76	27.655	22.916	25.825	1.00	37.41
519	C	SER	76	24.974	23.458	24.772	1.00	37.78
520	O	SER	76	24.695	23.072	23.636	1.00	37.04
521	N	TRP	77	24.376	22.980	25.859	1.00	38.01
522	CA	TRP	77	23.353	21.939	25.772	1.00	38.39
523	CB	TRP	77	23.104	21.321	27.147	1.00	38.69
524	CG	TRP	77	24.202	20.436	27.604	1.00	39.13
525	CD2	TRP	77	24.190	19.007	27.620	1.00	39.54
526	CE2	TRP	77	25.453	18.583	28.084	1.00	39.63
527	CE3	TRP	77	23.235	18.039	27.281	1.00	39.78
528	CD1	TRP	77	25.432	20.816	28.050	1.00	39.41
529	NE1	TRP	77	26.193	19.710	28.341	1.00	39.60
530	CZ2	TRP	77	25.790	17.235	28.223	1.00	39.93
531	CZ3	TRP	77	23.567	16.695	27.419	1.00	39.99
532	CH2	TRP	77	24.837	16.307	27.884	1.00	39.98
533	C	TRP	77	22.013	22.393	25.209	1.00	38.68
534	O	TRP	77	21.617	23.545	25.373	1.00	38.13
535	N	ARG	78	21.314	21.473	24.550	1.00	39.18
536	CA	ARG	78	20.000	21.779	24.006	1.00	40.02
537	CB	ARG	78	19.468	20.624	23.159	1.00	40.57
538	CG	ARG	78	20.303	20.287	21.948	1.00	41.52
539	CD	ARG	78	19.546	19.358	21.017	1.00	42.62
540	NE	ARG	78	20.367	18.942	19.884	1.00	43.50
541	CZ	ARG	78	19.899	18.314	18.810	1.00	44.17
542	NH1	ARG	78	18.609	18.027	18.716	1.00	44.45
543	NH2	ARG	78	20.725	17.971	17.830	1.00	44.49
544	C	ARG	78	19.072	21.978	25.194	1.00	40.35
545	O	ARG	78	19.370	21.521	26.300	1.00	40.15
546	N	GLN	79	17.950	22.654	24.972	1.00	40.81
547	CA	GLN	79	16.994	22.880	26.049	1.00	41.57
548	CB	GLN	79	15.840	23.763	25.561	1.00	42.48
549	CG	GLN	79	14.838	24.149	26.645	1.00	44.22
550	CD	GLN	79	15.473	24.908	27.798	1.00	45.14
551	OE1	GLN	79	14.780	25.377	28.700	1.00	46.06
552	NE2	GLN	79	16.796	25.030	27.776	1.00	45.97
553	C	GLN	79	16.480	21.509	26.476	1.00	41.41
554	O	GLN	79	16.296	20.621	25.641	1.00	41.16

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555	N	GLU	80	16.282	21.317	27.774	1.00	41.26
556	CA	GLU	80	15.805	20.028	28.242	1.00	41.34
557	CB	GLU	80	16.360	19.704	29.629	1.00	42.17
558	CG	GLU	80	17.053	18.345	29.680	1.00	43.75
559	CD	GLU	80	16.531	17.388	28.614	1.00	44.60
560	OE1	GLU	80	16.839	17.586	27.415	1.00	45.22
561	OE2	GLU	80	15.804	16.440	28.974	1.00	45.32
562	C	GLU	80	14.286	19.933	28.252	1.00	40.71
563	O	GLU	80	13.594	20.903	28.556	1.00	40.89
564	N	LYS	81	13.776	18.753	27.907	1.00	39.75
565	CA	LYS	81	12.335	18.527	27.863	1.00	38.73
566	CB	LYS	81	12.038	17.092	27.422	1.00	39.53
567	CG	LYS	81	12.528	16.771	26.017	1.00	40.66
568	CD	LYS	81	12.151	15.363	25.598	1.00	41.56
569	CE	LYS	81	12.619	15.066	24.183	1.00	42.08
570	NZ	LYS	81	12.261	13.672	23.798	1.00	43.00
571	C	LYS	81	11.663	18.812	29.202	1.00	37.41
572	O	LYS	81	10.620	19.468	29.253	1.00	37.57
573	N	ILE	82	12.256	18.318	30.283	1.00	35.76
574	CA	ILE	82	11.704	18.526	31.618	1.00	33.89
575	CB	ILE	82	11.863	17.257	32.484	1.00	34.19
576	CG2	ILE	82	11.265	17.493	33.870	1.00	34.32
577	CG1	ILE	82	11.204	16.059	31.789	1.00	34.07
578	CD1	ILE	82	9.717	16.249	31.495	1.00	34.19
579	C	ILE	82	12.428	19.678	32.300	1.00	32.44
580	O	ILE	82	13.619	19.582	32.583	1.00	32.31
581	N	THR	83	11.711	20.765	32.564	1.00	30.82
582	CA	THR	83	12.324	21.923	33.208	1.00	29.02
583	CB	THR	83	12.286	23.164	32.289	1.00	29.78
584	OG1	THR	83	10.924	23.520	32.027	1.00	30.24
585	CG2	THR	83	12.993	22.875	30.971	1.00	29.97
586	C	THR	83	11.699	22.313	34.547	1.00	27.39
587	O	THR	83	12.239	23.155	35.261	1.00	27.09
588	N	ARG	84	10.572	21.705	34.900	1.00	25.23
589	CA	ARG	84	9.920	22.040	36.164	1.00	23.24
590	CB	ARG	84	8.515	21.430	36.226	1.00	22.24
591	CG	ARG	84	8.492	19.925	36.443	1.00	21.26
592	CD	ARG	84	7.063	19.431	36.615	1.00	19.83
593	NE	ARG	84	6.265	19.571	35.397	1.00	19.28
594	CZ	ARG	84	6.217	18.667	34.421	1.00	19.38
595	NH1	ARG	84	5.458	18.882	33.354	1.00	20.14
596	NH2	ARG	84	6.920	17.546	34.511	1.00	18.88
597	C	ARG	84	10.726	21.568	37.373	1.00	22.25
598	O	ARG	84	11.520	20.628	37.284	1.00	22.14
599	N	THR	85	10.507	22.223	38.509	1.00	21.24
600	CA	THR	85	11.199	21.872	39.745	1.00	20.32
601	CB	THR	85	11.266	23.065	40.714	1.00	20.06
602	OG1	THR	85	9.938	23.413	41.132	1.00	18.89
603	CG2	THR	85	11.923	24.273	40.040	1.00	19.65
604	C	THR	85	10.447	20.755	40.454	1.00	20.32
605	O	THR	85	9.307	20.440	40.097	1.00	20.01
606	N	LYS	86	11.088	20.166	41.460	1.00	20.00
607	CA	LYS	86	10.479	19.096	42.240	1.00	20.26
608	CB	LYS	86	11.461	18.588	43.302	1.00	20.47
609	CG	LYS	86	10.952	17.395	44.112	1.00	20.87
610	CD	LYS	86	11.883	17.061	45.283	1.00	21.04

611	CE	LYS	86	13.251	16.587	44.805	1.00	21.03
612	NZ	LYS	86	14.149	16.246	45.963	1.00	20.00
613	C	LYS	86	9.228	19.644	42.925	1.00	20.34
614	O	LYS	86	8.204	18.970	43.009	1.00	19.85
615	N	GLU	87	9.328	20.877	43.412	1.00	21.05
616	CA	GLU	87	8.218	21.540	44.095	1.00	21.59
617	CB	GLU	87	8.662	22.931	44.559	1.00	23.73
618	CG	GLU	87	8.242	23.308	45.970	1.00	27.75
619	CD	GLU	87	8.596	24.748	46.313	1.00	29.66
620	OE1	GLU	87	8.108	25.662	45.613	1.00	31.10
621	OE2	GLU	87	9.363	24.969	47.277	1.00	31.37
622	C	GLU	87	7.013	21.668	43.158	1.00	20.66
623	O	GLU	87	5.871	21.408	43.548	1.00	20.58
624	N	GLU	88	7.273	22.073	41.920	1.00	19.90
625	CA	GLU	88	6.207	22.236	40.935	1.00	19.53
626	CB	GLU	88	6.751	22.936	39.685	1.00	20.43
627	CG	GLU	88	7.345	24.316	39.987	1.00	22.36
628	CD	GLU	88	7.932	25.004	38.767	1.00	23.16
629	OE1	GLU	88	8.612	24.333	37.966	1.00	23.49
630	OE2	GLU	88	7.728	26.228	38.618	1.00	24.89
631	C	GLU	88	5.613	20.877	40.575	1.00	18.58
632	O	GLU	88	4.407	20.753	40.363	1.00	17.85
633	N	ALA	89	6.466	19.858	40.520	1.00	17.78
634	CA	ALA	89	6.024	18.501	40.200	1.00	17.34
635	CB	ALA	89	7.236	17.580	40.028	1.00	16.41
636	C	ALA	89	5.121	17.970	41.311	1.00	16.99
637	O	ALA	89	4.104	17.322	41.045	1.00	17.06
638	N	LEU	90	5.496	18.239	42.559	1.00	16.95
639	CA	LEU	90	4.705	17.780	43.695	1.00	17.14
640	CB	LEU	90	5.448	18.036	45.015	1.00	17.39
641	CG	LEU	90	4.748	17.573	46.302	1.00	17.39
642	CD1	LEU	90	4.317	16.112	46.175	1.00	18.00
643	CD2	LEU	90	5.684	17.757	47.491	1.00	17.83
644	C	LEU	90	3.345	18.478	43.716	1.00	17.69
645	O	LEU	90	2.335	17.875	44.077	1.00	17.27
646	N	GLU	91	3.317	19.744	43.310	1.00	17.80
647	CA	GLU	91	2.069	20.496	43.292	1.00	18.89
648	CB	GLU	91	2.342	21.963	42.951	1.00	21.07
649	CG	GLU	91	1.173	22.894	43.219	1.00	25.71
650	CD	GLU	91	1.478	24.329	42.837	1.00	28.04
651	OE1	GLU	91	.813	25.247	43.368	1.00	30.67
652	OE2	GLU	91	2.378	24.544	41.995	1.00	30.50
653	C	GLU	91	1.120	19.882	42.266	1.00	17.66
654	O	GLU	91	-.080	19.749	42.514	1.00	17.03
655	N	LEU	92	1.662	19.507	41.110	1.00	16.95
656	CA	LEU	92	.862	18.886	40.058	1.00	16.30
657	CB	LEU	92	1.714	18.684	38.803	1.00	16.11
658	CG	LEU	92	2.036	19.966	38.033	1.00	16.73
659	CD1	LEU	92	3.163	19.720	37.043	1.00	16.34
660	CD2	LEU	92	.776	20.445	37.314	1.00	16.90
661	C	LEU	92	.328	17.541	40.548	1.00	15.92
662	O	LEU	92	-.846	17.207	40.350	1.00	16.13
663	N	ILE	93	1.198	16.774	41.194	1.00	15.17
664	CA	ILE	93	.819	15.473	41.725	1.00	14.90
665	CB	ILE	93	2.029	14.760	42.386	1.00	14.64
666	CG2	ILE	93	1.546	13.624	43.265	1.00	15.02

667	CG1	ILE	93	2.992	14.240	41.311	1.00	14.63
668	CD1	ILE	93	2.484	13.021	40.545	1.00	14.97
669	C	ILE	93	-.297	15.606	42.760	1.00	14.72
670	O	ILE	93	-1.256	14.835	42.744	1.00	13.96
671	N	ASN	94	-.167	16.569	43.668	1.00	14.85
672	CA	ASN	94	-1.189	16.748	44.691	1.00	15.33
673	CB	ASN	94	-.744	17.769	45.741	1.00	16.49
674	CG	ASN	94	.274	17.195	46.707	1.00	17.60
675	OD1	ASN	94	.176	16.035	47.103	1.00	18.59
676	ND2	ASN	94	1.250	18.007	47.100	1.00	18.55
677	C	ASN	94	-2.522	17.164	44.086	1.00	15.00
678	O	ASN	94	-3.578	16.753	44.564	1.00	14.46
679	N	GLY	95	-2.466	17.979	43.039	1.00	15.04
680	CA	GLY	95	-3.685	18.416	42.377	1.00	15.34
681	C	GLY	95	-4.395	17.252	41.706	1.00	15.58
682	O	GLY	95	-5.628	17.159	41.740	1.00	15.72
683	N	TYR	96	-3.625	16.361	41.083	1.00	15.31
684	CA	TYR	96	-4.209	15.194	40.418	1.00	15.14
685	CB	TYR	96	-3.133	14.421	39.638	1.00	14.76
686	CG	TYR	96	-2.507	15.178	38.480	1.00	14.80
687	CD1	TYR	96	-1.199	14.907	38.077	1.00	14.82
688	CE1	TYR	96	-.603	15.611	37.025	1.00	14.68
689	CD2	TYR	96	-3.213	16.173	37.795	1.00	14.83
690	CE2	TYR	96	-2.627	16.880	36.742	1.00	15.07
691	CZ	TYR	96	-1.322	16.597	36.364	1.00	15.37
692	OH	TYR	96	-.730	17.309	35.340	1.00	15.34
693	C	TYR	96	-4.851	14.277	41.464	1.00	15.43
694	O	TYR	96	-5.944	13.744	41.254	1.00	15.65
695	N	ILE	97	-4.173	14.095	42.593	1.00	15.43
696	CA	ILE	97	-4.696	13.251	43.663	1.00	15.72
697	CB	ILE	97	-3.694	13.190	44.853	1.00	15.76
698	CG2	ILE	97	-4.374	12.677	46.118	1.00	14.84
699	CG1	ILE	97	-2.506	12.300	44.465	1.00	15.25
700	CD1	ILE	97	-1.377	12.270	45.499	1.00	15.69
701	C	ILE	97	-6.047	13.794	44.133	1.00	16.67
702	O	ILE	97	-7.005	13.038	44.312	1.00	16.00
703	N	GLN	98	-6.123	15.107	44.310	1.00	17.89
704	CA	GLN	98	-7.356	15.741	44.762	1.00	19.99
705	CB	GLN	98	-7.097	17.229	45.041	1.00	21.22
706	CG	GLN	98	-8.316	18.042	45.451	1.00	24.46
707	CD	GLN	98	-9.163	18.456	44.265	1.00	26.01
708	OE1	GLN	98	-8.660	19.043	43.306	1.00	27.99
709	NE2	GLN	98	-10.457	18.160	44.325	1.00	27.84
710	C	GLN	98	-8.478	15.557	43.739	1.00	20.39
711	O	GLN	98	-9.612	15.240	44.101	1.00	20.54
712	N	LYS	99	-8.165	15.736	42.460	1.00	20.86
713	CA	LYS	99	-9.178	15.568	41.422	1.00	21.63
714	CB	LYS	99	-8.646	16.059	40.076	1.00	22.60
715	CG	LYS	99	-8.350	17.547	40.067	1.00	24.81
716	CD	LYS	99	-7.996	18.043	38.681	1.00	26.48
717	CE	LYS	99	-7.733	19.537	38.699	1.00	27.73
718	NZ	LYS	99	-7.488	20.068	37.328	1.00	29.53
719	C	LYS	99	-9.637	14.116	41.307	1.00	21.51
720	O	LYS	99	-10.804	13.845	41.013	1.00	21.72
721	N	ILE	100	-8.724	13.178	41.533	1.00	21.05
722	CA	ILE	100	-9.088	11.771	41.457	1.00	21.23

723	CB	ILE	100	-7.839	10.865	41.386	1.00	20.66
724	CG2	ILE	100	-8.255	9.395	41.410	1.00	20.61
725	CG1	ILE	100	-7.069	11.159	40.096	1.00	20.42
726	CD1	ILE	100	-5.754	10.417	39.975	1.00	19.93
727	C	ILE	100	-9.944	11.372	42.661	1.00	21.63
728	O	ILE	100	-10.955	10.685	42.509	1.00	21.63
729	N	LYS	101	-9.547	11.807	43.853	1.00	22.26
730	CA	LYS	101	-10.307	11.486	45.062	1.00	23.36
731	CB	LYS	101	-9.562	11.950	46.314	1.00	23.20
732	CG	LYS	101	-8.388	11.082	46.730	1.00	23.79
733	CD	LYS	101	-7.875	11.560	48.079	1.00	24.34
734	CE	LYS	101	-6.877	10.600	48.690	1.00	24.70
735	NZ	LYS	101	-6.498	11.046	50.064	1.00	23.81
736	C	LYS	101	-11.688	12.135	45.056	1.00	24.39
737	O	LYS	101	-12.651	11.566	45.574	1.00	24.32
738	N	SER	102	-11.782	13.327	44.474	1.00	25.07
739	CA	SER	102	-13.054	14.043	44.426	1.00	26.47
740	CB	SER	102	-12.819	15.541	44.216	1.00	25.83
741	OG	SER	102	-12.411	15.815	42.888	1.00	26.55
742	C	SER	102	-13.962	13.517	43.320	1.00	27.01
743	O	SER	102	-15.095	13.976	43.173	1.00	27.74
744	N	GLY	103	-13.464	12.557	42.547	1.00	27.70
745	CA	GLY	103	-14.251	11.994	41.464	1.00	28.32
746	C	GLY	103	-14.384	12.963	40.307	1.00	28.85
747	O	GLY	103	-15.220	12.786	39.422	1.00	28.97
748	N	GLU	104	-13.548	13.994	40.315	1.00	29.48
749	CA	GLU	104	-13.563	15.002	39.269	1.00	30.20
750	CB	GLU	104	-12.844	16.257	39.771	1.00	31.32
751	CG	GLU	104	-13.397	17.559	39.234	1.00	33.04
752	CD	GLU	104	-12.662	18.766	39.785	1.00	33.86
753	OE1	GLU	104	-12.786	19.045	40.997	1.00	34.38
754	OE2	GLU	104	-11.951	19.430	39.002	1.00	34.72
755	C	GLU	104	-12.882	14.458	38.007	1.00	30.26
756	O	GLU	104	-13.263	14.801	36.888	1.00	30.35
757	N	GLU	105	-11.883	13.601	38.206	1.00	30.18
758	CA	GLU	105	-11.130	12.981	37.114	1.00	30.07
759	CB	GLU	105	-9.756	13.642	36.959	1.00	31.02
760	CG	GLU	105	-9.746	15.029	36.351	1.00	32.41
761	CD	GLU	105	-10.173	15.032	34.898	1.00	33.59
762	OE1	GLU	105	-9.852	14.063	34.177	1.00	34.67
763	OE2	GLU	105	-10.819	16.011	34.474	1.00	34.33
764	C	GLU	105	-10.909	11.498	37.399	1.00	29.47
765	O	GLU	105	-10.869	11.082	38.556	1.00	28.99
766	N	ASP	106	-10.759	10.712	36.336	1.00	28.81
767	CA	ASP	106	-10.505	9.277	36.450	1.00	28.64
768	CB	ASP	106	-11.174	8.529	35.291	1.00	30.47
769	CG	ASP	106	-10.814	7.049	35.247	1.00	32.34
770	OD1	ASP	106	-10.010	6.585	36.082	1.00	34.04
771	OD2	ASP	106	-11.339	6.344	34.360	1.00	34.29
772	C	ASP	106	-8.986	9.096	36.381	1.00	27.37
773	O	ASP	106	-8.313	9.782	35.614	1.00	26.92
774	N	PHE	107	-8.451	8.185	37.190	1.00	26.16
775	CA	PHE	107	-7.012	7.929	37.209	1.00	25.20
776	CB	PHE	107	-6.696	6.709	38.081	1.00	24.24
777	CG	PHE	107	-5.224	6.472	38.281	1.00	23.95
778	CD1	PHE	107	-4.544	7.093	39.323	1.00	23.66

779	CD2	PHE	107	-4.511	5.647	37.414	1.00	24.12
780	CE1	PHE	107	-3.175	6.898	39.502	1.00	24.18
781	CE2	PHE	107	-3.141	5.447	37.583	1.00	23.65
782	CZ	PHE	107	-2.473	6.074	38.630	1.00	23.73
783	C	PHE	107	-6.465	7.669	35.808	1.00	24.77
784	O	PHE	107	-5.519	8.318	35.371	1.00	24.13
785	N	GLU	108	-7.063	6.702	35.117	1.00	25.00
786	CA	GLU	108	-6.628	6.321	33.777	1.00	25.31
787	CB	GLU	108	-7.537	5.220	33.217	1.00	27.41
788	CG	GLU	108	-7.681	4.007	34.121	1.00	30.11
789	CD	GLU	108	-6.406	3.684	34.874	1.00	31.74
790	OE1	GLU	108	-5.317	3.749	34.266	1.00	33.45
791	OE2	GLU	108	-6.492	3.356	36.075	1.00	33.16
792	C	GLU	108	-6.577	7.480	32.795	1.00	24.42
793	O	GLU	108	-5.633	7.596	32.009	1.00	23.83
794	N	SER	109	-7.595	8.333	32.829	1.00	23.77
795	CA	SER	109	-7.636	9.477	31.928	1.00	23.12
796	CB	SER	109	-8.978	10.202	32.044	1.00	23.92
797	OG	SER	109	-10.028	9.358	31.614	1.00	26.22
798	C	SER	109	-6.498	10.444	32.227	1.00	22.01
799	O	SER	109	-5.798	10.879	31.316	1.00	21.55
800	N	LEU	110	-6.310	10.778	33.500	1.00	20.63
801	CA	LEU	110	-5.241	11.694	33.878	1.00	19.76
802	CB	LEU	110	-5.321	12.040	35.370	1.00	20.30
803	CG	LEU	110	-6.340	13.107	35.789	1.00	20.86
804	CD1	LEU	110	-6.242	13.339	37.290	1.00	20.75
805	CD2	LEU	110	-6.075	14.407	35.037	1.00	21.02
806	C	LEU	110	-3.869	11.106	33.556	1.00	18.88
807	O	LEU	110	-2.967	11.827	33.134	1.00	17.78
808	N	ALA	111	-3.709	9.801	33.755	1.00	17.96
809	CA	ALA	111	-2.432	9.153	33.454	1.00	17.91
810	CB	ALA	111	-2.477	7.686	33.851	1.00	18.09
811	C	ALA	111	-2.172	9.283	31.954	1.00	17.72
812	O	ALA	111	-1.098	9.704	31.520	1.00	17.17
813	N	SER	112	-3.168	8.923	31.159	1.00	17.81
814	CA	SER	112	-3.037	9.028	29.715	1.00	18.41
815	CB	SER	112	-4.328	8.570	29.035	1.00	19.02
816	OG	SER	112	-4.387	9.068	27.711	1.00	21.29
817	C	SER	112	-2.739	10.466	29.293	1.00	18.43
818	O	SER	112	-1.971	10.709	28.368	1.00	18.42
819	N	GLN	113	-3.340	11.424	29.982	1.00	18.81
820	CA	GLN	113	-3.151	12.824	29.624	1.00	19.37
821	CB	GLN	113	-4.337	13.641	30.133	1.00	21.64
822	CG	GLN	113	-5.682	13.134	29.647	1.00	25.68
823	CD	GLN	113	-6.845	13.873	30.284	1.00	27.75
824	OE1	GLN	113	-7.061	15.054	30.020	1.00	29.55
825	NE2	GLN	113	-7.594	13.181	31.138	1.00	29.42
826	C	GLN	113	-1.859	13.491	30.083	1.00	18.45
827	O	GLN	113	-1.195	14.176	29.298	1.00	17.89
828	N	PHE	114	-1.488	13.284	31.342	1.00	17.63
829	CA	PHE	114	-.303	13.944	31.878	1.00	16.49
830	CB	PHE	114	-.716	14.812	33.075	1.00	16.64
831	CG	PHE	114	-1.748	15.854	32.744	1.00	16.37
832	CD1	PHE	114	-3.079	15.677	33.104	1.00	16.38
833	CD2	PHE	114	-1.390	17.008	32.056	1.00	16.56
834	CE1	PHE	114	-4.041	16.634	32.783	1.00	16.78

835	CE2	PHE	114	-2.346	17.972	31.729	1.00	16.83
836	CZ	PHE	114	-3.673	17.783	32.094	1.00	16.82
837	C	PHE	114	.925	13.123	32.275	1.00	16.31
838	O	PHE	114	1.980	13.699	32.530	1.00	15.70
839	N	SER	115	.826	11.799	32.334	1.00	15.56
840	CA	SER	115	2.004	11.031	32.739	1.00	15.15
841	CB	SER	115	1.680	9.541	32.869	1.00	14.74
842	OG	SER	115	2.809	8.848	33.368	1.00	14.19
843	C	SER	115	3.186	11.198	31.790	1.00	15.11
844	O	SER	115	3.035	11.125	30.568	1.00	14.46
845	N	ASP	116	4.367	11.415	32.367	1.00	15.77
846	CA	ASP	116	5.585	11.578	31.588	1.00	16.46
847	CB	ASP	116	6.574	12.501	32.308	1.00	17.13
848	CG	ASP	116	6.096	13.936	32.370	1.00	17.71
849	OD1	ASP	116	5.608	14.444	31.338	1.00	17.42
850	OD2	ASP	116	6.227	14.560	33.448	1.00	17.33
851	C	ASP	116	6.266	10.240	31.315	1.00	16.84
852	O	ASP	116	7.328	10.201	30.696	1.00	16.78
853	N	CYS	117	5.662	9.152	31.783	1.00	17.14
854	CA	CYS	117	6.219	7.819	31.561	1.00	17.56
855	CB	CYS	117	5.750	6.852	32.659	1.00	17.77
856	SG	CYS	117	6.249	5.108	32.431	1.00	16.67
857	C	CYS	117	5.743	7.322	30.199	1.00	18.18
858	O	CYS	117	4.696	7.739	29.716	1.00	18.41
859	N	SER	118	6.512	6.438	29.576	1.00	18.50
860	CA	SER	118	6.112	5.912	28.279	1.00	18.95
861	CB	SER	118	7.211	5.016	27.696	1.00	18.49
862	OG	SER	118	7.559	3.980	28.595	1.00	21.13
863	C	SER	118	4.804	5.129	28.402	1.00	18.40
864	O	SER	118	4.129	4.903	27.406	1.00	18.98
865	N	SER	119	4.444	4.730	29.621	1.00	17.70
866	CA	SER	119	3.210	3.978	29.839	1.00	17.55
867	CB	SER	119	3.231	3.296	31.216	1.00	17.12
868	OG	SER	119	3.409	4.232	32.267	1.00	17.70
869	C	SER	119	1.943	4.824	29.694	1.00	17.65
870	O	SER	119	.832	4.303	29.762	1.00	17.04
871	N	ALA	120	2.102	6.129	29.493	1.00	18.34
872	CA	ALA	120	.940	6.996	29.326	1.00	19.11
873	CB	ALA	120	1.382	8.434	29.025	1.00	18.80
874	C	ALA	120	.094	6.456	28.177	1.00	20.07
875	O	ALA	120	-1.124	6.587	28.183	1.00	20.60
876	N	LYS	121	.760	5.839	27.205	1.00	21.40
877	CA	LYS	121	.113	5.270	26.029	1.00	23.04
878	CB	LYS	121	1.174	4.772	25.033	1.00	24.04
879	CG	LYS	121	2.375	4.003	25.643	1.00	26.30
880	CD	LYS	121	1.952	3.082	26.821	1.00	27.30
881	CE	LYS	121	2.768	1.783	26.870	1.00	27.75
882	NZ	LYS	121	3.627	1.586	28.056	1.00	27.81
883	C	LYS	121	-.839	4.120	26.350	1.00	22.95
884	O	LYS	121	-1.779	3.854	25.594	1.00	23.43
885	N	ALA	122	-.577	3.442	27.462	1.00	22.05
886	CA	ALA	122	-1.381	2.313	27.893	1.00	21.66
887	CB	ALA	122	-.478	1.124	28.197	1.00	21.46
888	C	ALA	122	-2.202	2.680	29.120	1.00	21.15
889	O	ALA	122	-2.392	1.857	30.012	1.00	20.73
890	N	ARG	123	-2.674	3.924	29.159	1.00	21.13

891	CA	ARG	123	-3.487	4.411	30.268	1.00	21.04
892	CB	ARG	123	-4.824	3.665	30.297	1.00	23.15
893	CG	ARG	123	-5.581	3.701	28.958	1.00	26.27
894	CD	ARG	123	-6.304	5.022	28.731	1.00	28.68
895	NE	ARG	123	-7.714	4.953	29.113	1.00	31.32
896	CZ	ARG	123	-8.507	6.012	29.256	1.00	32.33
897	NH1	ARG	123	-8.028	7.233	29.058	1.00	32.20
898	NH2	ARG	123	-9.787	5.851	29.583	1.00	33.68
899	C	ARG	123	-2.774	4.251	31.611	1.00	19.65
900	O	ARG	123	-3.415	4.092	32.648	1.00	19.56
901	N	GLY	124	-1.446	4.288	31.580	1.00	18.71
902	CA	GLY	124	-.655	4.173	32.798	1.00	17.23
903	C	GLY	124	-.310	2.772	33.278	1.00	16.46
904	O	GLY	124	.450	2.614	34.229	1.00	15.56
905	N	ASP	125	-.844	1.753	32.615	1.00	15.86
906	CA	ASP	125	-.594	.367	33.020	1.00	15.68
907	CB	ASP	125	-1.498	-.572	32.217	1.00	15.08
908	CG	ASP	125	-1.275	-2.038	32.558	1.00	15.67
909	OD1	ASP	125	-1.217	-2.377	33.760	1.00	15.93
910	OD2	ASP	125	-1.168	-2.850	31.618	1.00	15.30
911	C	ASP	125	.863	-.082	32.886	1.00	15.76
912	O	ASP	125	1.488	.081	31.834	1.00	16.52
913	N	LEU	126	1.395	-.648	33.964	1.00	15.57
914	CA	LEU	126	2.766	-1.146	33.991	1.00	15.90
915	CB	LEU	126	3.484	-.651	35.248	1.00	15.81
916	CG	LEU	126	3.767	.852	35.318	1.00	16.01
917	CD1	LEU	126	4.334	1.196	36.682	1.00	16.63
918	CD2	LEU	126	4.742	1.244	34.226	1.00	16.49
919	C	LEU	126	2.786	-2.668	33.973	1.00	16.16
920	O	LEU	126	3.852	-3.279	33.877	1.00	16.15
921	N	GLY	127	1.605	-3.273	34.075	1.00	16.31
922	CA	GLY	127	1.508	-4.724	34.073	1.00	16.75
923	C	GLY	127	1.758	-5.324	35.443	1.00	17.20
924	O	GLY	127	1.926	-4.597	36.424	1.00	17.15
925	N	ALA	128	1.779	-6.651	35.515	1.00	17.39
926	CA	ALA	128	2.009	-7.342	36.778	1.00	17.94
927	CB	ALA	128	1.258	-8.663	36.801	1.00	17.86
928	C	ALA	128	3.497	-7.580	36.985	1.00	18.17
929	O	ALA	128	4.215	-7.941	36.057	1.00	18.00
930	N	PHE	129	3.953	-7.374	38.213	1.00	18.92
931	CA	PHE	129	5.358	-7.557	38.534	1.00	19.63
932	CB	PHE	129	6.089	-6.216	38.391	1.00	19.19
933	CG	PHE	129	5.499	-5.103	39.222	1.00	19.33
934	CD1	PHE	129	5.909	-4.905	40.537	1.00	19.45
935	CD2	PHE	129	4.529	-4.261	38.691	1.00	18.82
936	CE1	PHE	129	5.365	-3.883	41.309	1.00	19.62
937	CE2	PHE	129	3.975	-3.232	39.458	1.00	19.34
938	CZ	PHE	129	4.395	-3.044	40.770	1.00	19.20
939	C	PHE	129	5.542	-8.126	39.938	1.00	20.48
940	O	PHE	129	4.605	-8.161	40.738	1.00	19.68
941	N	SER	130	6.754	-8.590	40.222	1.00	21.37
942	CA	SER	130	7.075	-9.151	41.527	1.00	22.50
943	CB	SER	130	7.598	-10.579	41.370	1.00	23.11
944	OG	SER	130	8.770	-10.584	40.576	1.00	25.03
945	C	SER	130	8.155	-8.272	42.136	1.00	22.77
946	O	SER	130	8.659	-7.363	41.477	1.00	22.66

947	N	ARG	131	8.509	-8.530	43.391	1.00	23.44
948	CA	ARG	131	9.550	-7.737	44.029	1.00	24.18
949	CB	ARG	131	9.692	-8.102	45.514	1.00	24.60
950	CG	ARG	131	8.690	-7.390	46.429	1.00	24.92
951	CD	ARG	131	8.964	-7.684	47.898	1.00	25.89
952	NE	ARG	131	8.045	-7.001	48.809	1.00	25.89
953	CZ	ARG	131	8.074	-5.700	49.089	1.00	26.18
954	NH1	ARG	131	8.979	-4.910	48.531	1.00	26.31
955	NH2	ARG	131	7.201	-5.189	49.949	1.00	26.33
956	C	ARG	131	10.865	-7.967	43.300	1.00	24.35
957	O	ARG	131	11.130	-9.064	42.806	1.00	24.95
958	N	GLY	132	11.673	-6.917	43.215	1.00	24.52
959	CA	GLY	132	12.954	-7.020	42.546	1.00	24.41
960	C	GLY	132	13.016	-6.358	41.183	1.00	24.47
961	O	GLY	132	14.109	-6.127	40.664	1.00	24.98
962	N	GLN	133	11.866	-6.029	40.603	1.00	24.01
963	CA	GLN	133	11.840	-5.414	39.280	1.00	24.09
964	CB	GLN	133	10.650	-5.964	38.485	1.00	25.36
965	CG	GLN	133	10.490	-7.481	38.581	1.00	27.91
966	CD	GLN	133	9.305	-7.997	37.785	1.00	29.24
967	OE1	GLN	133	8.879	-9.140	37.957	1.00	30.80
968	NE2	GLN	133	8.770	-7.158	36.906	1.00	30.42
969	C	GLN	133	11.798	-3.880	39.267	1.00	23.46
970	O	GLN	133	12.546	-3.239	38.524	1.00	23.29
971	N	MET	134	10.931	-3.290	40.085	1.00	22.84
972	CA	MET	134	10.794	-1.836	40.116	1.00	22.46
973	CB	MET	134	9.330	-1.463	40.381	1.00	22.33
974	CG	MET	134	8.329	-2.175	39.480	1.00	22.57
975	SD	MET	134	8.509	-1.770	37.735	1.00	22.72
976	CE	MET	134	6.809	-2.014	37.162	1.00	23.57
977	C	MET	134	11.680	-1.161	41.155	1.00	22.47
978	O	MET	134	12.193	-1.805	42.069	1.00	22.23
979	N	GLN	135	11.867	.145	40.998	1.00	22.42
980	CA	GLN	135	12.670	.901	41.946	1.00	22.64
981	CB	GLN	135	12.683	2.382	41.574	1.00	23.26
982	CG	GLN	135	13.270	2.615	40.192	1.00	25.02
983	CD	GLN	135	13.510	4.077	39.867	1.00	26.07
984	OE1	GLN	135	13.288	4.510	38.735	1.00	27.62
985	NE2	GLN	135	13.982	4.840	40.845	1.00	26.79
986	C	GLN	135	12.040	.673	43.310	1.00	22.39
987	O	GLN	135	10.815	.698	43.449	1.00	21.57
988	N	LYS	136	12.877	.445	44.310	1.00	21.82
989	CA	LYS	136	12.401	.143	45.652	1.00	22.11
990	CB	LYS	136	13.565	.175	46.640	1.00	23.42
991	CG	LYS	136	13.260	-.609	47.893	1.00	25.21
992	CD	LYS	136	12.851	-2.034	47.540	1.00	26.76
993	CE	LYS	136	12.573	-2.843	48.787	1.00	28.18
994	NZ	LYS	136	13.821	-2.976	49.592	1.00	29.70
995	C	LYS	136	11.232	.948	46.214	1.00	21.09
996	O	LYS	136	10.268	.373	46.704	1.00	21.01
997	N	PRO	137	11.302	2.291	46.167	1.00	20.21
998	CD	PRO	137	12.365	3.166	45.647	1.00	20.15
999	CA	PRO	137	10.193	3.083	46.716	1.00	19.51
1000	CB	PRO	137	10.629	4.523	46.449	1.00	19.89
1001	CG	PRO	137	12.127	4.428	46.429	1.00	20.23
1002	C	PRO	137	8.868	2.759	46.020	1.00	18.62

1003	O	PRO	137	7.817	2.672	46.661	1.00	18.20
1004	N	PHE	138	8.938	2.595	44.707	1.00	17.72
1005	CA	PHE	138	7.768	2.274	43.901	1.00	17.29
1006	CB	PHE	138	8.139	2.291	42.417	1.00	17.12
1007	CG	PHE	138	6.953	2.201	41.496	1.00	17.38
1008	CD1	PHE	138	6.373	3.355	40.974	1.00	16.83
1009	CD2	PHE	138	6.394	.967	41.178	1.00	16.68
1010	CE1	PHE	138	5.250	3.281	40.149	1.00	17.12
1011	CE2	PHE	138	5.271	.879	40.354	1.00	17.47
1012	CZ	PHE	138	4.696	2.039	39.838	1.00	17.04
1013	C	PHE	138	7.274	.885	44.285	1.00	16.99
1014	O	PHE	138	6.086	.667	44.492	1.00	16.19
1015	N	GLU	139	8.208	-.058	44.362	1.00	17.23
1016	CA	GLU	139	7.889	-1.432	44.718	1.00	18.00
1017	CB	GLU	139	9.166	-2.282	44.707	1.00	19.53
1018	CG	GLU	139	8.970	-3.704	45.210	1.00	21.62
1019	CD	GLU	139	10.276	-4.473	45.287	1.00	22.41
1020	OE1	GLU	139	10.939	-4.611	44.243	1.00	23.16
1021	OE2	GLU	139	10.636	-4.936	46.391	1.00	23.77
1022	C	GLU	139	7.237	-1.505	46.099	1.00	17.75
1023	O	GLU	139	6.179	-2.111	46.258	1.00	17.76
1024	N	ASP	140	7.860	-.882	47.095	1.00	17.78
1025	CA	ASP	140	7.305	-.922	48.446	1.00	17.66
1026	CB	ASP	140	8.205	-.178	49.438	1.00	18.48
1027	CG	ASP	140	9.500	-.922	49.724	1.00	20.16
1028	OD1	ASP	140	9.547	-2.146	49.487	1.00	20.57
1029	OD2	ASP	140	10.465	-.285	50.198	1.00	20.81
1030	C	ASP	140	5.893	-.356	48.512	1.00	17.24
1031	O	ASP	140	5.028	-.928	49.174	1.00	16.78
1032	N	ALA	141	5.655	.756	47.822	1.00	16.59
1033	CA	ALA	141	4.329	1.367	47.825	1.00	16.42
1034	CB	ALA	141	4.371	2.723	47.108	1.00	16.12
1035	C	ALA	141	3.310	.446	47.152	1.00	16.18
1036	O	ALA	141	2.218	.228	47.670	1.00	15.84
1037	N	SER	142	3.678	-.109	46.004	1.00	16.24
1038	CA	SER	142	2.777	-.991	45.267	1.00	16.71
1039	CB	SER	142	3.431	-1.444	43.959	1.00	16.49
1040	OG	SER	142	3.743	-.330	43.142	1.00	16.91
1041	C	SER	142	2.325	-2.219	46.054	1.00	17.13
1042	O	SER	142	1.144	-2.569	46.031	1.00	16.83
1043	N	PHE	143	3.258	-2.879	46.738	1.00	17.55
1044	CA	PHE	143	2.911	-4.069	47.506	1.00	18.32
1045	CB	PHE	143	4.152	-4.939	47.748	1.00	18.72
1046	CG	PHE	143	4.538	-5.785	46.563	1.00	18.96
1047	CD1	PHE	143	5.342	-5.272	45.550	1.00	19.25
1048	CD2	PHE	143	4.058	-7.087	46.441	1.00	19.32
1049	CE1	PHE	143	5.663	-6.042	44.429	1.00	19.01
1050	CE2	PHE	143	4.372	-7.865	45.328	1.00	19.64
1051	CZ	PHE	143	5.177	-7.339	44.318	1.00	19.59
1052	C	PHE	143	2.213	-3.769	48.827	1.00	18.37
1053	O	PHE	143	1.638	-4.664	49.443	1.00	18.84
1054	N	ALA	144	2.247	-2.510	49.254	1.00	18.17
1055	CA	ALA	144	1.597	-2.112	50.498	1.00	17.95
1056	CB	ALA	144	2.399	-1.000	51.182	1.00	18.19
1057	C	ALA	144	.167	-1.640	50.220	1.00	17.93
1058	O	ALA	144	-.640	-1.499	51.134	1.00	17.53

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1059	N	LEU	145	-.139	-1.395	48.949	1.00	17.94
1060	CA	LEU	145	-1.474	-.953	48.559	1.00	18.09
1061	CB	LEU	145	-1.440	-.284	47.178	1.00	16.75
1062	CG	LEU	145	-.837	1.111	46.984	1.00	15.85
1063	CD1	LEU	145	-.739	1.411	45.483	1.00	15.41
1064	CD2	LEU	145	-1.701	2.155	47.678	1.00	14.65
1065	C	LEU	145	-2.447	-2.123	48.490	1.00	19.06
1066	O	LEU	145	-2.059	-3.253	48.185	1.00	19.29
1067	N	ARG	146	-3.713	-1.845	48.776	1.00	20.08
1068	CA	ARG	146	-4.751	-2.863	48.687	1.00	21.58
1069	CB	ARG	146	-5.877	-2.568	49.683	1.00	23.06
1070	CG	ARG	146	-5.442	-2.667	51.143	1.00	25.52
1071	CD	ARG	146	-6.600	-2.442	52.115	1.00	27.91
1072	NE	ARG	146	-6.944	-1.031	52.289	1.00	30.12
1073	CZ	ARG	146	-6.149	-.126	52.855	1.00	30.64
1074	NH1	ARG	146	-4.954	-.478	53.306	1.00	31.21
1075	NH2	ARG	146	-6.551	1.136	52.977	1.00	30.51
1076	C	ARG	146	-5.267	-2.771	47.252	1.00	21.55
1077	O	ARG	146	-5.127	-1.728	46.611	1.00	21.50
1078	N	THR	147	-5.845	-3.850	46.736	1.00	21.82
1079	CA	THR	147	-6.356	-3.824	45.371	1.00	21.75
1080	CB	THR	147	-6.987	-5.173	44.977	1.00	22.35
1081	OG1	THR	147	-6.022	-6.216	45.148	1.00	23.67
1082	CG2	THR	147	-7.432	-5.150	43.517	1.00	22.54
1083	C	THR	147	-7.397	-2.721	45.235	1.00	21.57
1084	O	THR	147	-8.273	-2.568	46.093	1.00	21.33
1085	N	GLY	148	-7.282	-1.946	44.162	1.00	21.20
1086	CA	GLY	148	-8.206	-.852	43.922	1.00	21.52
1087	C	GLY	148	-7.825	.438	44.628	1.00	21.37
1088	O	GLY	148	-8.462	1.470	44.421	1.00	21.83
1089	N	GLU	149	-6.782	.394	45.452	1.00	21.48
1090	CA	GLU	149	-6.355	1.580	46.187	1.00	21.18
1091	CB	GLU	149	-5.910	1.204	47.592	1.00	23.06
1092	CG	GLU	149	-6.997	.637	48.458	1.00	27.36
1093	CD	GLU	149	-6.646	.784	49.912	1.00	29.17
1094	OE1	GLU	149	-5.438	.649	50.235	1.00	30.95
1095	OE2	GLU	149	-7.564	1.031	50.719	1.00	30.75
1096	C	GLU	149	-5.250	2.390	45.528	1.00	19.76
1097	O	GLU	149	-4.413	1.858	44.800	1.00	19.17
1098	N	MET	150	-5.247	3.684	45.825	1.00	18.25
1099	CA	MET	150	-4.277	4.609	45.262	1.00	17.36
1100	CB	MET	150	-5.018	5.784	44.616	1.00	17.96
1101	CG	MET	150	-4.147	6.714	43.792	1.00	18.98
1102	SD	MET	150	-5.159	7.958	42.963	1.00	19.91
1103	CE	MET	150	-5.513	9.037	44.338	1.00	20.33
1104	C	MET	150	-3.291	5.117	46.309	1.00	16.27
1105	O	MET	150	-3.628	5.282	47.484	1.00	15.78
1106	N	SER	151	-2.062	5.355	45.871	1.00	15.57
1107	CA	SER	151	-1.020	5.843	46.758	1.00	14.93
1108	CB	SER	151	.361	5.460	46.221	1.00	15.00
1109	OG	SER	151	.711	6.276	45.108	1.00	14.45
1110	C	SER	151	-1.076	7.355	46.843	1.00	14.66
1111	O	SER	151	-1.894	8.005	46.187	1.00	14.43
1112	N	GLY	152	-.201	7.895	47.682	1.00	14.44
1113	CA	GLY	152	-.060	9.329	47.813	1.00	14.23
1114	C	GLY	152	1.151	9.584	46.929	1.00	14.07

1115	O	GLY	152	1.486	8.719	46.117	1.00	13.85
1116	N	PRO	153	1.834	10.732	47.047	1.00	13.81
1117	CD	PRO	153	1.567	11.893	47.909	1.00	14.08
1118	CA	PRO	153	3.003	10.974	46.191	1.00	13.84
1119	CB	PRO	153	3.334	12.450	46.448	1.00	13.38
1120	CG	PRO	153	2.047	13.018	47.044	1.00	13.70
1121	C	PRO	153	4.161	10.057	46.577	1.00	14.03
1122	O	PRO	153	4.572	10.020	47.741	1.00	14.66
1123	N	VAL	154	4.675	9.314	45.600	1.00	14.71
1124	CA	VAL	154	5.797	8.404	45.828	1.00	14.79
1125	CB	VAL	154	5.437	6.959	45.409	1.00	15.18
1126	CG1	VAL	154	6.634	6.032	45.607	1.00	15.52
1127	CG2	VAL	154	4.247	6.470	46.236	1.00	14.82
1128	C	VAL	154	6.990	8.897	45.020	1.00	15.40
1129	O	VAL	154	6.890	9.104	43.809	1.00	14.90
1130	N	PHE	155	8.116	9.084	45.702	1.00	15.88
1131	CA	PHE	155	9.330	9.586	45.072	1.00	16.85
1132	CB	PHE	155	10.039	10.583	46.001	1.00	17.49
1133	CG	PHE	155	9.217	11.793	46.354	1.00	18.25
1134	CD1	PHE	155	8.147	11.695	47.241	1.00	18.99
1135	CD2	PHE	155	9.520	13.036	45.807	1.00	19.18
1136	CE1	PHE	155	7.393	12.820	47.578	1.00	19.38
1137	CE2	PHE	155	8.771	14.165	46.137	1.00	19.00
1138	CZ	PHE	155	7.707	14.054	47.024	1.00	19.28
1139	C	PHE	155	10.328	8.498	44.689	1.00	16.84
1140	O	PHE	155	10.687	7.658	45.511	1.00	17.06
1141	N	THR	156	10.769	8.526	43.435	1.00	17.24
1142	CA	THR	156	11.773	7.588	42.938	1.00	17.69
1143	CB	THR	156	11.190	6.512	42.009	1.00	17.45
1144	OG1	THR	156	10.941	7.083	40.716	1.00	17.11
1145	CG2	THR	156	9.903	5.939	42.592	1.00	17.57
1146	C	THR	156	12.748	8.410	42.106	1.00	18.21
1147	O	THR	156	12.569	9.615	41.941	1.00	17.61
1148	N	ASP	157	13.769	7.758	41.560	1.00	19.14
1149	CA	ASP	157	14.743	8.470	40.739	1.00	20.09
1150	CB	ASP	157	15.943	7.571	40.428	1.00	21.20
1151	CG	ASP	157	16.756	7.241	41.659	1.00	22.93
1152	OD1	ASP	157	16.937	8.141	42.506	1.00	23.42
1153	OD2	ASP	157	17.227	6.088	41.773	1.00	24.37
1154	C	ASP	157	14.133	8.971	39.434	1.00	19.98
1155	O	ASP	157	14.681	9.869	38.794	1.00	20.41
1156	N	SER	158	12.998	8.396	39.044	1.00	19.65
1157	CA	SER	158	12.327	8.786	37.807	1.00	19.83
1158	CB	SER	158	11.439	7.643	37.312	1.00	20.57
1159	OG	SER	158	12.219	6.492	37.041	1.00	23.13
1160	C	SER	158	11.491	10.048	37.972	1.00	19.02
1161	O	SER	158	11.217	10.757	36.999	1.00	18.55
1162	N	GLY	159	11.093	10.328	39.208	1.00	17.78
1163	CA	GLY	159	10.286	11.505	39.472	1.00	17.03
1164	C	GLY	159	9.286	11.207	40.569	1.00	16.43
1165	O	GLY	159	9.567	10.407	41.460	1.00	16.29
1166	N	ILE	160	8.121	11.844	40.507	1.00	15.62
1167	CA	ILE	160	7.084	11.637	41.512	1.00	14.89
1168	CB	ILE	160	6.565	12.983	42.066	1.00	14.36
1169	CG2	ILE	160	5.645	12.739	43.259	1.00	14.26
1170	CG1	ILE	160	7.747	13.854	42.495	1.00	14.60

1171	CD1	ILE	160	7.355	15.255	42.946	1.00	14.29
1172	C	ILE	160	5.930	10.876	40.872	1.00	14.51
1173	O	ILE	160	5.481	11.224	39.781	1.00	15.18
1174	N	HIS	161	5.454	9.844	41.562	1.00	14.32
1175	CA	HIS	161	4.371	9.002	41.053	1.00	14.23
1176	CB	HIS	161	4.795	7.531	40.978	1.00	13.67
1177	CG	HIS	161	6.083	7.274	40.268	1.00	13.42
1178	CD2	HIS	161	6.349	6.572	39.145	1.00	13.14
1179	ND1	HIS	161	7.305	7.675	40.768	1.00	14.45
1180	CE1	HIS	161	8.268	7.222	39.981	1.00	12.95
1181	NE2	HIS	161	7.713	6.549	38.990	1.00	14.57
1182	C	HIS	161	3.113	8.968	41.906	1.00	14.30
1183	O	HIS	161	3.136	9.235	43.109	1.00	14.27
1184	N	ILE	162	2.021	8.589	41.250	1.00	13.69
1185	CA	ILE	162	.743	8.347	41.902	1.00	14.50
1186	CB	ILE	162	-.414	9.222	41.362	1.00	15.56
1187	CG2	ILE	162	-1.737	8.736	41.951	1.00	16.82
1188	CG1	ILE	162	-.196	10.687	41.749	1.00	16.35
1189	CD1	ILE	162	-1.233	11.644	41.171	1.00	16.45
1190	C	ILE	162	.550	6.913	41.411	1.00	14.01
1191	O	ILE	162	.600	6.665	40.206	1.00	14.21
1192	N	ILE	163	.368	5.972	42.330	1.00	13.61
1193	CA	ILE	163	.210	4.569	41.958	1.00	13.49
1194	CB	ILE	163	1.260	3.691	42.700	1.00	13.35
1195	CG2	ILE	163	1.145	2.239	42.249	1.00	13.23
1196	CG1	ILE	163	2.671	4.218	42.420	1.00	13.78
1197	CD1	ILE	163	3.759	3.586	43.286	1.00	14.45
1198	C	ILE	163	-1.180	4.012	42.263	1.00	13.81
1199	O	ILE	163	-1.732	4.253	43.335	1.00	13.97
1200	N	LEU	164	-1.743	3.273	41.310	1.00	13.55
1201	CA	LEU	164	-3.048	2.643	41.498	1.00	13.95
1202	CB	LEU	164	-4.055	3.124	40.445	1.00	14.06
1203	CG	LEU	164	-5.422	2.418	40.500	1.00	14.34
1204	CD1	LEU	164	-6.142	2.783	41.794	1.00	14.67
1205	CD2	LEU	164	-6.255	2.811	39.291	1.00	14.93
1206	C	LEU	164	-2.873	1.136	41.350	1.00	14.53
1207	O	LEU	164	-2.492	.662	40.284	1.00	14.17
1208	N	ARG	165	-3.128	.383	42.416	1.00	15.12
1209	CA	ARG	165	-3.011	-1.064	42.318	1.00	16.57
1210	CB	ARG	165	-2.804	-1.702	43.692	1.00	16.92
1211	CG	ARG	165	-2.585	-3.201	43.588	1.00	17.58
1212	CD	ARG	165	-2.461	-3.883	44.936	1.00	18.44
1213	NE	ARG	165	-2.613	-5.326	44.772	1.00	19.76
1214	CZ	ARG	165	-2.697	-6.197	45.772	1.00	20.62
1215	NH1	ARG	165	-2.638	-5.777	47.028	1.00	20.16
1216	NH2	ARG	165	-2.864	-7.490	45.511	1.00	19.98
1217	C	ARG	165	-4.321	-1.562	41.712	1.00	17.15
1218	O	ARG	165	-5.395	-1.313	42.252	1.00	17.41
1219	N	THR	166	-4.225	-2.256	40.587	1.00	18.06
1220	CA	THR	166	-5.407	-2.757	39.905	1.00	19.03
1221	CB	THR	166	-5.322	-2.487	38.392	1.00	18.87
1222	OG1	THR	166	-4.147	-3.109	37.857	1.00	18.93
1223	CG2	THR	166	-5.265	-.992	38.123	1.00	19.36
1224	C	THR	166	-5.606	-4.249	40.115	1.00	19.82
1225	O	THR	166	-6.648	-4.797	39.762	1.00	19.31
1226	N	GLU	167	-4.609	-4.906	40.695	1.00	21.11

1227	CA	GLU	167	-4.704	-6.343	40.918	1.00	22.25
1228	CB	GLU	167	-4.465	-7.055	39.593	1.00	23.79
1229	CG	GLU	167	-4.677	-8.545	39.604	1.00	27.14
1230	CD	GLU	167	-4.283	-9.153	38.278	1.00	28.69
1231	OE1	GLU	167	-4.592	-8.539	37.235	1.00	30.03
1232	OE2	GLU	167	-3.667	-10.238	38.277	1.00	30.37
1233	C	GLU	167	-3.684	-6.816	41.945	1.00	21.79
1234	O	GLU	167	-2.642	-6.145	42.090	1.00	21.19
1235	OT	GLU	167	-3.931	-7.864	42.577	1.00	21.37
1236	CB	TYR	170	7.118	13.530	52.814	1.00	55.56
1237	CG	TYR	170	5.703	13.351	52.248	1.00	56.20
1238	CD1	TYR	170	4.952	12.203	52.521	1.00	56.47
1239	CE1	TYR	170	3.645	12.044	52.017	1.00	56.62
1240	CD2	TYR	170	5.114	14.339	51.451	1.00	56.44
1241	CE2	TYR	170	3.807	14.189	50.943	1.00	56.66
1242	CZ	TYR	170	3.081	13.043	51.231	1.00	56.70
1243	OH	TYR	170	1.793	12.904	50.754	1.00	57.13
1244	C	TYR	170	6.194	14.920	54.642	1.00	54.37
1245	O	TYR	170	5.970	13.961	55.356	1.00	54.42
1246	N	TYR	170	8.641	14.888	54.282	1.00	55.08
1247	CA	TYR	170	7.303	14.840	53.619	1.00	54.90
1248	N	SEP	171	5.893	16.138	54.270	1.00	53.40
1249	CA	SEP	171	4.911	16.155	55.342	1.00	52.46
1250	CB	SEP	171	4.976	17.400	56.248	1.00	53.58
1251	OG	SEP	171	5.418	17.088	57.603	1.00	55.25
1252	C	SEP	171	3.548	15.967	54.667	1.00	50.95
1253	O	SEP	171	3.041	16.860	53.999	1.00	50.72
1254	P	SEP	171	4.475	17.349	58.906	1.00	56.21
1255	O1P	SEP	171	5.346	17.261	60.120	1.00	56.25
1256	O2P	SEP	171	4.006	18.761	58.948	1.00	56.33
1257	O3P	SEP	171	3.279	16.493	58.749	1.00	56.44
1258	N	PRO	172	2.718	14.784	54.962	1.00	49.69
1259	CD	PRO	172	3.094	13.822	56.010	1.00	49.43
1260	CA	PRO	172	1.410	14.432	54.383	1.00	48.40
1261	CB	PRO	172	1.020	13.160	55.148	1.00	48.84
1262	CG	PRO	172	1.752	13.280	56.446	1.00	49.09
1263	C	PRO	172	.290	15.467	54.378	1.00	47.21
1264	O	PRO	172	.229	16.373	55.213	1.00	46.73
1265	N	THR	173	-.610	15.312	53.417	1.00	45.94
1266	CA	THR	173	-1.744	16.207	53.287	1.00	44.92
1267	CB	THR	173	-1.980	16.579	51.817	1.00	45.05
1268	OG1	THR	173	-.722	16.601	51.131	1.00	45.35
1269	CG2	THR	173	-2.601	17.960	51.713	1.00	45.23
1270	C	THR	173	-2.965	15.472	53.824	1.00	44.00
1271	O	THR	173	-3.048	14.246	53.740	1.00	43.67
1272	N	SEP	174	-3.901	16.219	54.394	1.00	43.11
1273	CA	SEP	174	-5.107	15.613	54.928	1.00	42.34
1274	CB	SEP	174	-5.982	16.661	55.613	1.00	41.77
1275	OG	SEP	174	-5.285	17.278	56.677	1.00	40.78
1276	C	SEP	174	-5.859	14.947	53.788	1.00	42.13
1277	O	SEP	174	-5.803	15.405	52.648	1.00	42.16
1278	P	SEP	174	-5.017	18.848	56.671	1.00	40.24
1279	O1P	SEP	174	-3.939	19.053	57.657	1.00	39.89
1280	O2P	SEP	174	-4.410	19.263	55.377	1.00	40.27
1281	O3P	SEP	174	-6.331	19.526	56.783	1.00	40.16
1282	N	PRO	175	-6.571	13.850	54.079	1.00	42.06

1283	CD	PRO	175	-6.744	13.234	55.405	1.00	41.84
1284	CA	PRO	175	-7.333	13.122	53.058	1.00	41.94
1285	CB	PRO	175	-8.043	12.029	53.862	1.00	41.89
1286	CG	PRO	175	-8.070	12.566	55.257	1.00	42.04
1287	C	PRO	175	-8.289	13.969	52.217	1.00	42.11
1288	O	PRO	175	-8.502	13.678	51.039	1.00	42.01
1289	N	SER	176	-8.863	15.011	52.812	1.00	42.14
1290	CA	SER	176	-9.777	15.887	52.081	1.00	42.14
1291	CB	SER	176	-11.199	15.310	52.073	1.00	42.12
1292	OG	SER	176	-11.820	15.434	53.340	1.00	41.96
1293	C	SER	176	-9.791	17.273	52.709	1.00	42.33
1294	O	SER	176	-9.105	17.452	53.738	1.00	42.23
1295	OT	SER	176	-10.485	18.159	52.167	1.00	42.54
1296	OH2	WAT	200	2.014	6.388	33.070	1.00	13.93
1297	OH2	WAT	201	-1.283	-2.300	28.997	1.00	15.35
1298	OH2	WAT	202	-2.992	-1.687	35.759	1.00	21.83
1299	OH2	WAT	203	-2.513	19.277	39.236	1.00	14.45
1300	OH2	WAT	204	-6.092	9.665	81.760	1.00	17.79
1301	OH2	WAT	205	1.926	17.345	34.818	1.00	15.51
1302	OH2	WAT	206	-2.638	.254	52.032	1.00	18.20
1303	OH2	WAT	207	11.754	22.376	44.104	1.00	20.03
1304	OH2	WAT	208	9.320	-4.615	42.075	1.00	21.68
1305	OH2	WAT	209	4.413	10.176	28.305	1.00	24.86
1306	OH2	WAT	210	3.500	15.584	33.508	1.00	17.17
1307	OH2	WAT	211	3.016	-.603	29.684	1.00	16.24
1308	OH2	WAT	212	-3.433	-.744	29.090	1.00	20.34
1309	OH2	WAT	213	-3.928	16.386	47.143	1.00	19.86
1310	OH2	WAT	214	-1.492	19.796	34.357	1.00	23.80
1311	OH2	WAT	215	5.749	17.029	31.175	1.00	17.04
1312	OH2	WAT	216	-7.589	4.674	47.250	1.00	24.91
1313	OH2	WAT	217	5.836	-2.876	50.964	1.00	22.06
1314	OH2	WAT	218	11.848	8.037	47.950	1.00	23.46
1315	OH2	WAT	219	12.348	13.307	37.042	1.00	20.57
1316	OH2	WAT	220	-4.113	9.169	47.403	1.00	23.76
1317	OH2	WAT	221	5.203	22.317	35.018	1.00	22.18
1318	OH2	WAT	222	9.525	6.324	30.502	1.00	26.39
1319	OH2	WAT	223	-10.609	9.339	53.354	1.00	30.61
1320	OH2	WAT	224	-3.990	10.308	49.848	1.00	21.74
1321	OH2	WAT	225	9.853	25.698	42.396	1.00	29.89
1322	OH2	WAT	226	-6.397	11.568	75.148	1.00	21.91
1323	OH2	WAT	227	7.548	3.839	49.241	1.00	24.61
1324	OH2	WAT	228	-6.083	4.855	51.274	1.00	23.65
1325	OH2	WAT	229	-6.550	7.286	50.590	1.00	23.55
1326	OH2	WAT	230	.976	11.832	28.657	1.00	18.86
1327	OH2	WAT	231	-5.723	7.029	48.100	1.00	26.00
1328	OH2	WAT	232	3.126	23.015	39.476	1.00	21.91
1329	OH2	WAT	233	-10.950	13.155	65.324	1.00	25.05
1330	OH2	WAT	234	-2.711	12.584	49.681	1.00	29.21
1331	OH2	WAT	235	7.434	-10.766	44.709	1.00	25.02
1332	OH2	WAT	236	-4.201	1.994	25.179	1.00	21.85
1333	OH2	WAT	237	-2.892	14.979	79.350	1.00	29.32
1334	OH2	WAT	238	14.239	5.232	43.399	1.00	27.32
1335	OH2	WAT	239	-3.070	-1.184	54.587	1.00	30.22
1336	OH2	WAT	240	-11.964	9.420	40.306	1.00	24.61
1337	OH2	WAT	241	-2.664	20.784	36.612	1.00	25.57
1338	OH2	WAT	242	15.679	.913	43.518	1.00	32.81

1339	OH2	WAT	243	1.248	-.885	54.817	1.00	24.39
1340	OH2	WAT	244	-8.178	4.883	76.583	1.00	26.66
1341	OH2	WAT	245	-6.075	15.256	48.229	1.00	27.33
1342	OH2	WAT	246	-4.529	1.584	33.651	1.00	26.47
1343	OH2	WAT	247	-1.823	14.652	48.096	1.00	27.21
1344	OH2	WAT	248	-10.286	7.153	39.164	1.00	24.26
1345	OH2	WAT	249	8.150	8.218	48.429	1.00	23.48
1346	OH2	WAT	250	-8.406	2.586	77.882	1.00	25.81
1347	OH2	WAT	251	13.368	-6.143	46.515	1.00	38.51
1348	OH2	WAT	252	-.009	23.620	39.303	1.00	36.19
1349	OH2	WAT	253	-9.460	14.934	66.850	1.00	34.00
1350	OH2	WAT	254	-3.751	20.245	45.512	1.00	37.11
1351	OH2	WAT	255	12.681	10.291	34.535	1.00	26.21
1352	OH2	WAT	256	6.777	.601	58.270	1.00	32.10
1353	OH2	WAT	257	8.803	20.438	32.878	1.00	28.86
1354	OH2	WAT	258	.450	6.445	65.189	1.00	30.51
1355	OH2	WAT	259	-16.448	9.387	39.020	1.00	41.90
1356	OH2	WAT	260	15.918	6.602	36.928	1.00	43.42
1357	OH2	WAT	261	-8.987	4.515	44.837	1.00	34.46
1358	OH2	WAT	262	6.985	13.991	29.119	1.00	26.21
1359	OH2	WAT	263	-7.897	-7.308	39.485	1.00	38.23
1360	OH2	WAT	264	6.735	8.681	53.846	1.00	30.04
1361	OH2	WAT	265	-7.201	10.978	28.692	1.00	40.13
1362	OH2	WAT	266	-11.277	11.811	33.774	1.00	34.24
1363	OH2	WAT	267	-5.570	16.341	27.209	1.00	27.61
1364	OH2	WAT	268	28.978	19.691	29.458	1.00	34.54
1365	OH2	WAT	269	-.394	-3.182	56.909	1.00	37.28
1366	OH2	WAT	270	-5.901	-6.275	48.732	1.00	38.98
1367	OH2	WAT	271	-5.314	13.550	50.350	1.00	28.96
1368	OH2	WAT	272	17.572	7.657	45.251	1.00	37.08
1369	OH2	WAT	273	1.725	.998	24.485	1.00	41.72
1370	OH2	WAT	274	14.327	-4.819	37.245	1.00	37.09
1371	OH2	WAT	275	6.276	11.721	57.649	1.00	47.33
1372	OH2	WAT	276	-15.076	17.669	59.792	1.00	40.97
1373	OH2	WAT	277	-.429	-2.499	53.645	1.00	33.17
1374	OH2	WAT	278	3.038	-3.057	54.799	1.00	39.54
1375	OH2	WAT	279	-3.954	9.216	72.671	1.00	39.85
1376	OH2	WAT	280	-10.200	1.398	41.849	1.00	42.94
1377	OH2	WAT	281	-10.292	3.217	52.063	1.00	43.76
1378	OH2	WAT	282	-15.225	12.071	60.987	1.00	45.57
1379	OH2	WAT	283	4.001	-4.280	52.274	1.00	29.89
1380	OH2	WAT	284	-8.055	-8.627	42.074	1.00	41.79
1381	OH2	WAT	285	-1.008	-6.151	62.404	1.00	46.22
1382	OH2	WAT	286	-9.176	10.031	51.259	1.00	36.18
1383	OH2	WAT	287	-3.447	5.807	27.025	1.00	39.54
1384	OH2	WAT	288	6.178	1.935	27.972	1.00	41.27
1385	OH2	WAT	289	-.878	11.803	51.809	1.00	31.35
1386	OH2	WAT	290	4.340	.648	60.998	1.00	32.63
1387	OH2	WAT	291	7.811	-2.038	52.827	1.00	36.03
1388	OH2	WAT	292	-8.166	18.423	67.710	1.00	38.02
1389	OH2	WAT	293	-14.604	10.287	35.634	1.00	45.62
1390	OH2	WAT	294	-10.474	20.227	53.859	1.00	46.74
1391	OH2	WAT	295	17.892	23.932	22.437	1.00	42.17
1392	OH2	WAT	296	17.145	17.710	24.729	1.00	47.54
1393	OH2	WAT	297	1.480	20.841	46.728	1.00	36.92
1394	OH2	WAT	298	-10.284	6.137	64.005	1.00	46.42

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1395	OH2	WAT	299	3.682	3.530	62.317	1.00	44.53
1396	OH2	WAT	300	-2.017	-8.476	51.591	1.00	45.29
1397	OH2	WAT	301	-.106	11.221	83.869	1.00	37.74
1398	OH2	WAT	302	-8.555	9.470	27.344	1.00	50.52
1399	OH2	WAT	303	6.694	27.979	40.780	1.00	40.54
1400	OH2	WAT	304	-9.496	-4.420	47.793	1.00	40.89
1401	OH2	WAT	305	-15.396	11.041	56.150	1.00	44.20
1402	OH2	WAT	306	-5.928	-11.415	43.389	1.00	48.32
1403	OH2	WAT	307	-10.479	-7.663	44.866	1.00	52.88
1404	OH2	WAT	308	14.262	4.179	49.470	1.00	46.97
1405	OH2	WAT	309	-.041	15.184	62.705	1.00	40.11
1406	OH2	WAT	310	15.939	3.184	44.811	1.00	44.49
1407	OH2	WAT	311	3.817	-.929	63.168	1.00	42.13
1408	OH2	WAT	312	-10.174	-.055	47.822	1.00	44.73
1409	OH2	WAT	313	13.924	-.156	50.669	1.00	43.49
1410	OH2	WAT	314	4.943	21.521	46.064	1.00	33.15
1411	OH2	WAT	315	-4.990	11.627	72.769	1.00	42.40
1412	OH2	WAT	316	-8.733	15.608	48.610	1.00	49.94
1413	OH2	WAT	317	-7.762	17.938	49.355	1.00	40.62
1414	OH2	WAT	318	-4.978	-.433	31.726	1.00	37.41
1415	OH2	WAT	319	-4.689	22.825	55.686	1.00	47.23
1416	OH2	WAT	320	11.750	-10.644	40.083	1.00	48.25
1417	OH2	WAT	321	-10.564	18.537	57.762	1.00	37.40
1418	OH2	WAT	322	7.490	10.973	25.298	1.00	45.18
1419	OH2	WAT	323	2.274	12.065	76.050	1.00	38.17
1420	OH2	WAT	324	-2.115	17.289	58.628	1.00	41.95
1421	OH2	WAT	325	16.399	18.887	20.072	1.00	48.74
1422	OH2	WAT	326	20.050	19.008	27.094	1.00	45.30
1423	OH2	WAT	327	-10.935	-4.259	42.863	1.00	52.28
1424	OH2	WAT	328	-5.431	-5.213	36.216	1.00	35.64
1425	OH2	WAT	329	-9.928	22.834	64.306	1.00	45.77
1426	OH2	WAT	330	-8.275	6.285	42.925	1.00	42.06
1427	OH2	WAT	331	-13.049	17.206	57.668	1.00	38.15
1428	OH2	WAT	332	5.624	-10.159	35.555	1.00	40.21
1429	OH2	WAT	333	23.293	26.941	32.316	1.00	48.27
1430	OH2	WAT	334	1.567	.896	62.295	1.00	37.23
1431	OH2	WAT	335	-13.988	-1.533	56.782	1.00	49.02
1432	OH2	WAT	336	6.259	13.631	61.216	1.00	40.35
1433	OH2	WAT	337	-9.939	-2.809	49.680	1.00	50.64
1434	OH2	WAT	338	-10.829	10.035	61.256	1.00	39.01
1435	OH2	WAT	339	16.685	10.608	37.337	1.00	48.68
1436	OH2	WAT	340	-8.780	.857	55.000	1.00	42.72
1437	OH2	WAT	341	-8.843	-3.223	40.067	1.00	36.16
1438	OH2	WAT	342	.612	11.479	80.681	1.00	45.15
1439	OH2	WAT	343	1.599	-2.462	63.176	1.00	45.28
1440	OH2	WAT	344	18.905	21.201	43.743	1.00	46.85
1441	OH2	WAT	345	9.154	-12.805	43.973	1.00	45.21
1442	OH2	WAT	346	-8.708	18.686	55.960	1.00	41.01
1443	OH2	WAT	347	-3.987	-7.989	48.762	1.00	44.36
1444	OH2	WAT	348	-2.038	-9.706	42.264	1.00	40.86
1445	OH2	WAT	349	-11.305	11.929	49.565	1.00	45.07
1446	OH2	WAT	350	3.795	3.399	77.919	1.00	48.57
1447	OH2	WAT	351	8.628	9.813	50.645	1.00	39.75

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Note to Table 1 - Coordinates from restrained individual B-factor refinement, refinement resolution: 62.017 - 1.840 A; starting r= .2597; free_r= .2866; final r= .2444; free_r= .2708; B rmsd for bonded mainchain atoms=.846; target= 1.5; B rmsd for bonded sidechain atoms= .985; target= 2.0; B rmsd for angle mainchain atoms= 1.551; target= 2.0; B rmsd for angle sidechain atoms= 1.623; target= 2.5; wa= 1.17512; rweight=.530173; target= mlf; steps= 30; space group = $P2_12_12_1$ (a= 35.270; b= 43.903; c= 124.659; $\alpha=\beta=\gamma=90°$); B-correction resolution: 6.0 - 1.840; initial B-factor correction applied to fobs: B11= -1.655; B22= -3.389; B33= 5.044; B12= .000; B13= .000; B23= .000; B-factor correction applied to coordinate array B: 2.789; bulk solvent: density level= .377734 e/A^3; B-factor= 30.924 A^2 reflections with |Fobs|/sigma_F < 0.0 rejected reflections with |Fobs| > 10000 * rms(Fobs) rejected theoretical total number of reflections in resolution range: 17526 (100.0 %) number of unobserved reflections (no entry or |F|=0): 419 (2.4 %) number of reflections rejected: 0 (0.0 %) total number of reflections used: 17107 (97.6 %) number of reflections in working set: 16241 (92.7 %); number of reflections in test set: 866 (4.9 %)CRYST1 35.270 43.903 124.659 90.00 90.00 90.00 P 21 21 21.

The human Pin1 numbering sequence differs from that above due to the addition of four residues at the N-terminus from the E.coli cloning/expression vector. Thus, one should add 4 to the native human Pin1 sequence to arrive at the numbering scheme above. For instance, Trp11 of the original sequence is now Trp15 above.

In addition, in accordance with this invention, WW domains, Pin1 WW domains, or Pin1 WW domain mutants may be crystallized in co-complex with known WW domain binding agents, substrates, or inhibitors. The crystal structures of a series of such complexes may then be solved by molecular replacement and compared with that of a wild-type WW domain. Potential sites for modification within the various binding sites of the WW domain may thus be identified. This information provides an additional tool for determining the most efficient binding interactions, for example, increased hydrophobic interactions, between a WW domain and a chemical entity or compound.

All of the complexes referred to above may be studied using well-known X-ray diffraction techniques and may be refined versus 2-3 Å resolution X-ray data to an R value of about 0.20 or less using computer software, such as X-PLOR (Yale University, 1992, distributed by Molecular Simulations, Inc.). See, *e.g.*, Blundel & Johnson, *supra*; Methods in Enzymology, vol. 114 and 115, H. W. Wyckoff *et al.*, eds., Academic Press (1985). This information may thus be used to optimize known classes of WW domain

binding agents (*e.g.*, inhibitors), and to design and synthesize novel classes of WW domain binding agents (*e.g.*, inhibitors).

The design of binding agents that bind or otherwise associate with or inhibit a WW domain according to the invention generally involves consideration of two factors. First, the compound or binding agent must be capable of physically and structurally associating with a WW domain. Non-covalent molecular interactions important in the association of a WW domain with a substrate include hydrogen bonding, van der Waals and hydrophobic interactions.

Second, the compound or binding agent must be able to assume a conformation that allows it to associate with a WW domain. Although certain portions of the compound or binding agent will not directly participate in this association, those portions may still influence the overall conformation of the molecule. This, in turn, may have a significant impact on potency. Such conformational requirements include the overall three-dimensional structure and orientation of the chemical entity or compound in relation to all or a portion of the binding site, *e.g.*, active site or accessory binding site of a WW domain (*e.g.*, a Pin1 WW domain), or the spacing between functional groups of a compound comprising several chemical entities that directly interact with a WW domain.

The potential inhibitory or binding effect of a chemical compound on a WW domain may be analyzed prior to its actual synthesis and testing by the use of computer modeling techniques. If the theoretical structure of the given compound suggests insufficient interaction and association between it and a WW domain, synthesis and testing of the compound may be obviated. However, if computer modeling indicates a strong interaction, the molecule may then be tested for its ability to bind to a WW domain. Methods of assaying for WW domain activity are known in the art. Methods for assaying the effect of a potential binding agent can be performed in the presence of a known binding agent of a WW domain. For example, the effect of the potential binding agent can be assayed by measuring the ability of the potential binding agent to compete with a known binding agent.

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An inhibitory or other binding compound of a WW domain may be computationally evaluated and designed by means of a series of steps in which chemical entities or fragments are screened and selected for their ability to associate with the individual binding pockets or other areas of a WW domain.

One skilled in the art may use one of several methods to screen chemical entities or fragments for their ability to associate with a WW domain and more particularly with the individual binding pockets of the WW domain of Pin1. This process may begin by visual inspection of, for example, the active site on the computer screen based on the Pin1 WW domain coordinates in Table 1. Selected fragments or chemical entities may then be positioned in a variety of orientations, or docked, within an individual binding pocket of a WW domain. Docking may be accomplished using software such as Quanta and Sybyl, followed by energy minimization and molecular dynamics with standard molecular mechanics forcefields, such as CHARMM and AMBER.

Specialized computer programs may also assist in the process of selecting fragments or chemical entities. These include:

1. GRID (Goodford, P. J., "A Computational Procedure for Determining Energetically Favorable Binding Sites on Biologically Important Macromolecules", J. Med. Chem., 28, pp. 849-857 (1985)). GRID is available from Oxford University, Oxford, UK.

2. MCSS (Miranker, A. and M. Karplus, "Functionality Maps of Binding Sites: A Multiple Copy Simultaneous Search Method." Proteins: Structure. Function and Genetics, 11, pp. 29-34 (1991)). MCSS is available from Molecular Simulations, Burlington, Mass.

3. AUTODOCK (Goodsell, D. S. and A. J. Olsen, "Automated Docking of Substrates to Proteins by Simulated Annealing", Proteins: Structure. Function, and Genetics, 8, pp. 195-202 (1990)). AUTODOCK is available from Scripps Research Institute, La Jolla, Calif.

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4. DOCK (Kuntz, I. D. *et al.*, "A Geometric Approach to Macromolecule-Ligand Interactions", J. Mol. Biol., 161, pp. 269-288 (1982)). DOCK is available from University of California, San Francisco, Calif.

Once suitable chemical entities or fragments have been selected, they can be assembled into a single compound or binding agent (*e.g.*, an inhibitor). Assembly may be performed by visual inspection of the relationship of the fragments to each other on the three-dimensional image displayed on a computer screen in relation to the structure coordinates of the Pin1 WW domain as set forth in Table 1. This would be followed by manual model building using software such as Quanta or Sybyl.

Useful programs to aid one of skill in the art in connecting the individual chemical entities or fragments include:

1. CAVEAT (Bartlett, P. A. et al, "CAVEAT: A Program to Facilitate the Structure-Derived Design of Biologically Active Molecules". In "Molecular Recognition in Chemical and Biological Problems", Special Pub., Royal Chem. Soc., 78, pp. 182-196 (1989)). CAVEAT is available from the University of California, Berkeley, Calif.

2. 3D Database systems such as MACCS-3D (MDL Information Systems, San Leandro, Calif.). This area is reviewed in Martin, Y. C., "3D Database Searching in Drug Design", J. Med. Chem., 35, pp. 2145-2154 (1992)).

3. HOOK (available from Molecular Simulations, Burlington, Mass.).

In addition to the method of building or identifing a WW domain binding agent in a step-wise fashion one fragment or chemical entity at a time as described above, inhibitory or other WW domain binding compounds may be designed as a whole or "de novo" using either an empty active site or optionally including some portion(s) of a known inhibitor(s). These methods include:

1. LUDI (Bohm, H.-J., "The Computer Program LUDI: A New Method for the De Novo Design of Enzyme Inhibitors", J. Comp. Aid. Molec. Design, 6, pp. 61-78 (1992)). LUDI is available from Biosym Technologies, San Diego, Calif.

2. LEGEND (Nishibata, Y. and A. Itai, Tetrahedron, 47, p. 8985 (1991)). LEGEND is available from Molecular Simulations, Burlington, Mass.

3. LeapFrog (available from Tripos Associates, St. Louis, Mo.).

Other molecular modeling techniques may also be employed in accordance with this invention. See, *e.g.*, Cohen, N. C. *et al.*, "Molecular Modeling Software and Methods for Medicinal Chemistry", J. Med. Chem., 33, pp. 883-894 (1990). See also, Navia, M. A. and M. A. Murcko, "The Use of Structural Information in Drug Design", Current Opinions in Structural Biology, 2, pp. 202-210 (1992).

Once a compound or binding agent has been designed or selected by the above methods, the efficiency with which that compound may bind to a WW domain may be tested and optimized by computational evaluation.

A compound designed or selected as a WW domain binding agent may be further computationally optimized so that in its bound state it would preferably lack repulsive electrostatic interaction with the target site. Such non-complementary (*e.g.*, electrostatic) interactions include repulsive charge-charge, dipole-dipole and charge-dipole interactions. Specifically, the sum of all electrostatic interactions between the binding agent and the WW domain when the binding agent is bound to the WW domain, preferably make a neutral or favorable contribution to the enthalpy of binding.

Specific computer software is available in the art to evaluate compound deformation energy and electrostatic interaction. Examples of programs designed for such uses include: Gaussian 92, revision C (M. J. Frisch, Gaussian, Inc., Pittsburgh, Pa., 1992); AMBER, version 4.0 (P. A. Kollman, University of California at San Francisco, 1994); QUANTA/CHARMM (Molecular Simulations, Inc., Burlington, Mass. 1994); and Insight II/Discover (Biosysm Technologies Inc., San Diego, Calif., 1994). These programs may be implemented, for example, using a Silicon Graphics workstation, IRIS 4D/35 or IBM RISC/6000 workstation model 550. Other hardware systems and software packages will be known to those skilled in the art of which the speed and capacity are continually modified

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Once a WW domain binding agent has been selected or designed, as described above, substitutions may then be made in some of its atoms or side groups in order to improve or modify its binding properties. Generally, initial substitutions are conservative, *e.g.*, the replacement group will have approximately the same size, shape, hydrophobicity and charge as the original group. Such substituted chemical compounds may then be analyzed for efficiency of fit to a WW domain by the same computer methods described above.

A further aspect of the invention encompasses methods of treatment using inhibitors or binding agents of a WW domain. The WW domain activity has been associated with a number of diseases including, for example, hypertension and muscular dystrophy (Staub and Rotin, Structure 4(5):495-9, 1996); and breast cancer (Bednarak *et al.*, Cancer Res., 60(8):2140-5, 2000).

Cell proliferative disorders contemplated for treatment using the invention compounds and methods disclosed herein include disorders characterized by unwanted, inappropriate or uncontrolled cell growth. Particular examples include cancer, fibrotic disorders, non-neoplastic growths such as benign prostatic hypertrophy, endometriosis, psoriasis, and the like. Cancers contemplated for treatment in accordance with the present invention include both solid tumors and hematopoeitic cancers such as leukemias and lymphomas.

Solid tumors that are treatable utilizing the invention compounds and methods include carcinomas, sarcomas, osteomas, fibrosarcomas, chondrosarcomas, and the like. Specific cancers contemplated for treatment include breast cancer, brain cancer, lung cancer (non-small cell and small cell), colon cancer, pancreatic cancer, prostate cancer, gastric cancer, bladder cancer, kidney cancer, head and neck cancer, and the like.

Fibrotic disorders are generally characterized by inappropriate overproliferation of non-cancerous fibroblasts. Examples include fibromyalgia, fibrosis (cystic, hepatic, idopathic pulmonary, pericardial, and the like), cardiac fibromas, fibromuscular hyperplasia, restenosis, atherosclerosis, fibromyositis, and the like.

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Invention compounds are additionally useful in inhibiting mitosis in pathogenic organisms and are, therefore, useful for treating infectious diseases. Particular infectious diseases treatable by the methods disclosed herein include bacterial infections and fungal infections.

Bacterial infections contemplated for treatment using invention compounds and methods include infections caused by both gram-positive and gram-negative bacteria, including infections caused by *Staphylococcus*, *Clostridium*, *Streptococcus, Enterococcus, Diplococcus, Hemophilus, Neisseria, Erysipelothricosis, Listeria, Bacillus, Salmonella, Shigella, Escherichia, Klebsiella, Enterobacter, Serratia, Proteus, Morganella, Providencia, Yersinia, Camphylobacter, Mycobacteria,* and the like. Infection by such organisms causes a wide variety of disorders including pneumonia, diarrhea and dysentery, anthrax, rheumatic fever, toxic shock syndrome, mastoiditis, meningitis, gonorrhea, typhoid fever, gastroenteritis, brucellosis, cholera, bubonic plague, tetanus, tuberculosis, Lyme disease, and the like.

Fungal infections contemplated for treatment using invention compounds and methods include systemic fungal infections, dermatophytoses and fungal infections of the genito-unrinary tract. Systemic fungal infections include those caused by *Histoplasma, Coccidioides, Cryptococcus, Blastocyces, Paracoccidioides, Candida, Aspergillus, Nocardia, Sporothrix, Rhizopus, Absidia, Mucor, Hormodendrum, Phialophora, Rhinosporidium*, and the like. Dermatophyte infections include those caused by *Microsporum, Trichophyton, Epidermophyton, Candida, Pityrosporum*, and the like. Fungal disorders of the genito-urinary tract include infections caused by *Candida, Cryptococcus, Aspergillus, Zygomycodoides*, and the like. Infection by such organisms causes a wide variety of disorders such as ringworm, thrush, San Joaquin fever or Valley fever, Gilcrist's disease, and the like. These infections can be particularly serious, and even fatal, in patients with a depressed immune system such as organ transplant recipients and persons with acquired immunodefficiency syndrome (AIDS).

In a further aspect of the invention, invention compounds may be used as insecticides. The compounds of the invention prevent mitosis in insect cells, and thus

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can be used to control the growth and proliferation of a variety of insect pests. This aspect of the invention has important applications in agriculture, such as in the field, in the storage of agricultural products, and the like. Additionally, invention compounds are useful for controlling insect populations in places inhabited by man, such as homes, offices, and the like.

The particular invention compound(s) selected for therapeutic use as taught herein can be administered to a subject either alone or in a pharmaceutical composition where the compound(s) is mixed with suitable carriers or excipient(s). In treating a subject, a therapeutically effective dose of compound (*i.e.*, active ingredient) is administered. A therapeutically effective dose refers to that amount of the active ingredient that produces amelioration of symptoms or a prolongation of survival of a subject.

Toxicity and therapeutic efficacy of a compound can be determined by standard pharmaceutical procedures in cell culture or experimental animals. Cell culture assays and animal studies can be used to determine the LD_{50} (the dose lethal to 50% of a population) and the ED_{50} (the dose therapeutically effective in 50% of a population). The dose ratio between toxic and therapeutic effects is the therapeutic index, which can be expressed as the ratio LD_{50}/ED_{50}. Compounds which exhibit large therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosages suitable for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon a variety of factors, *e.g.*, the dosage form employed, the route of administration utilized, the condition of the subject, and the like.

For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays by determining an IC_{50} (*i.e.*, the concentration of the test substance which achieves a half-maximal inhibition of PPIase activity). A dose can then be formulated in animal models to achieve a circulating plasma concentration range that includes the IC_{50} as determined

in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by HPLC. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See *e.g.* Fingl *et al.*, 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 pl).

It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity, to organ dysfunction, and the like. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administered dose in the management of the disorder of interest will vary with the severity of the condition to be treated, with the route of administration, and the like. The severity of the condition may, for example, be evaluated, in part, by standard prognostic evaluation methods. Further, the dose and perhaps dose frequency will also vary according to the age, body weight, and response of the individual patient. Typically, the dose will be between about 1-10 mg/kg of body weight. About 1 mg to about 50 mg will be administered to a child, and between about 25 mg and about 1000 mg will be administered to an adult. A program comparable to that discussed above may be used in veterinary medicine.

Depending on the specific conditions being treated, such agents may be formulated and administered systemically or locally. Techniques for formulation and administration may be found in "Remington's Pharmaceutical Sciences," 1990, 18th ed., Mack Publishing Co., Easton, PA. Suitable routes may include oral, rectal, transdermal, vaginal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections, just to name a few.

For injection, compounds of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration,

penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

Use of pharmaceutically acceptable carriers to formulate the compounds herein disclosed into dosages suitable for systemic administration is within the scope of the invention. With proper choice of carrier and suitable manufacturing practice, the compositions of the present invention, in particular those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be readily formulated using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, dragees, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject to be treated.

Agents intended to be administered intracellularly may be administered using techniques well known to those of ordinary skill in the art. For example, such agents may be encapsulated into liposomes, then administered as described above. Liposomes are spherical lipid bilayers with aqueous interiors. All molecules present in an aqueous solution at the time of liposome formation are incorporated into the aqueous interior. The liposomal contents are both protected from the external microenvironment and, because liposomes fuse with cell membranes, are efficiently delivered into the cell cytoplasm. Delivery systems involving liposomes are discussed in International Patent Publication No. WO 91/02805 and International Patent Publication No. WO 91/19501, as well as U.S. Patent No. 4,880,635 to Janoff *et al.* These publications and patents provide useful descriptions of techniques for liposome drug delivery and are incorporated by reference herein in their entirety.

Pharmaceutical compositions contemplated for use in the present invention include compositions wherein the active ingredients are contained in an amount effective to achieve the intended purpose. Determination of an effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

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In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, lyophilizing processes, or the like.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain compounds which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, dextran, or the like. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, sorbitol, and the like; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone (PVP), and the like, as well as mixtures of any two or more thereof. If desired, disintegrating agents may be added, such as cross-linked

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polyvinyl pyrrolidone, agar, alginic acid or a salt thereof such as sodium alginate, and the like.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, titanium dioxide, lacquer solutions, suitable organic solvents or solvent mixtures, and the like. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

The invention will now be described in greater detail by reference to the following non-limiting examples.

EXAMPLES

Protein purification and crystallography. His8-tagged Pin1 was expressed and purified by Ni^{+2}-chelation chromatography, the histidine tag was removed by thrombin digestion, and the protein purified as described in Ranganathan *et al.*, Cell 89:875-886, 1997. All site-directed mutants were constructed using the QuikChange (Stratagene) protocol and purified like wild type Pin1. Crystals of the Pin1-YpSPTpSPS complex were grown in hanging drops at 4 °C by mixing 1.0 µl of the Pin1-peptide complex with 1.0 µl of a reservoir solution containing 100 mM MOPSO-Na^+ (pH 7.0), 28% (v/v) PEG 8000, 2 mM DTT, stabilized in 100 mM MOPSO-Na^+ (pH 7.0), 25% (v/v) PEG 8000, 20% (v/v) glycerol, 1 mM DTT, and rapidly frozen in a 100 K stream of nitrogen gas. A native data set extending to 1.84 Å resolution was collected at the Stanford Synchrotron

Radiation Laboratory, beamline 9-1 (λ = 0.98 Å). Data were processed with DENZO and scaled with SCALEPACK (Otwinowski, Z., Minor, W. Meth. Enzymol. 276:307-326, 1997). The crystals contain one Pin1-peptide complex per asymmetric unit and belong to space group $P2_12_12_1$ (a = 35.27 Å, b = 43.90 Å, c = 124.66 Å, $\alpha = \beta = \gamma = 90^o$). The final data set with an overall R merge of 6.2 % (R merge = 33.7 % in the highest resolution shell) is 97.3 % complete (98.2 % in the highest resolution shell) for the resolution range of 62.02 Å to 1.84 Å. The structure of the Pin1-YpSPTpSPS repeat complex was solved by molecular replacement with AMORE (Navaza, J. Acta Crystallogr. A 50:157-163, 1994) using the Pin1 monomer as a starting model (Ranganathan *et al.*, Cell 89:875-886, 1997). The resulting model was then positionally refined against all the data between 62.02 Å and 1.84 Å using the default bulk solvent model in CNS with maximum likelihood targets (Brunger *et al.*, Acta Crystallogr. D 54:905-921, 1998). After refining the rebuilt model, water molecules were added automatically using CNS and edited manually in O. The final positional refinement converged to a crystallographic R factor of 24% (R free = 27%) for all data (17107 reflections) between 62.02 Å and 1.84 Å. This model consists of residues 1 to 38 and 51 to 163 of human Pin1, the entire phosphopeptide, and 151 water molecules. Model quality was checked with PROCHECK (Laskowski *et al.*, J. Appl. Crystallogr. 26:283-291, 1993). A total of 91.7% of the residues are in the most favored regions of the Ramachandran plot, 6.8% in the additional allowed region, and 0.8% in the generously allowed region. Glu-5 borders the generously allowed region.

Binding Analysis. To determine the affinity of full length Pin1 and its isolated PPIase and WW domains for a set of rhodamine-labeled peptides as shown in Table 2, were obtained commercially (SynPep Corporation, Dublin, CA) and allowed to interact with Pin1, PPIase and WW domains. These peptides were derived from proteins previously shown to interact with Pin1. While the set of peptides examined is limited, a consensus emerges from comparison of the highest affinity interactions. Lyophilized peptides were dissolved in 25 mM HEPES-Na^+ (pH 7.5), 100 mM NaCl, 1 mM DTT and stored for short periods of time at –20 °C. Peptides were labeled with the amine reactive reagent tetramethylrhodamine-5-(and-6)-isothiocyanate (Molecular Probes, Inc. Eugene, OR) using a 2:1 molar ratio of rhodamine to peptide in 0.1 M sodium bicarbonate (pH 9.0) at ambient temperature for 10 hr. Fluorescence data were collected

on a PTI Alphascan spectrofluorimeter (Photon Technology Instruments, Santa Clara, CA). Dissociation equilibrium constants for Pin1-peptide complexes were determined by measuring the change in fluorescence anisotropy of a set of peptide solutions at constant concentration of peptide each of which contained varied concentrations of Pin1 using the procedure described previously (Vinson *et al.*, Biochemistry 37:10871-10880, 1998). The core binding element determined from this group of peptides is PXpSP, where X cannot be Gly. Surprisingly, the best binding sequences differ from the consensus Pin1-binding sequence of WFYpSPR determined using a degenerate P.Ser-Pro anchored peptide library (Yaffe *et al.*, Science 278:1957-1960, 1997). Furthermore, the dissociation constants roughly segregate into two affinity groups, lower affinity interactions more typical of other WW domain-peptide complexes with dissociation constants greater than 50 μM and higher affinity interactions with dissociation constants less then 30 μM. Several of these peptides yielded crystalline specimens; the most well ordered crystals obtained thus far included the doubly phosphorylated CTD peptide, YpSPTpSPS.

Table 2 Dissociation equilibrium constants (μM) for Pin1-peptide complexes [a]

Labeled Peptide	Pin1	WW	PPIase
WFYSPFLE (Pintide) (SEQ ID NO:5)	>540	n.d.	n.d.
WFYpSPFLE (Pintide) (SEQ ID NO:6)	17±2.0	44±9.5	86±11
VPRpTPV (Cdc25c-T48) (SEQ ID NO:7)	4.9±1.1	7.7±3.3	n.b.
YLGpSPI (Cdc25c-S168) (SEQ ID NO:8)	69±10	91±30	> 400
LYRpSPS (Cdc25c-S214) (SEQ ID NO:9)	47±7.3	72±15	> 500
GSSpSPV (Wee1-S123) (SEQ ID NO:10)	73±4.9	n.d.	n.d.
PPApTPP (Myt1-T412) (SEQ ID NO:11)	12±2.1	15±4.7	n.b.
PPGpSPP (Myt1-S416) (SEQ ID NO:12)	80±18	126±21	n.b.
STSpTPR (Myt1-T455) (SEQ ID NO:13)	46±6.5	39±12	n.b.
YSPTSPS (CTD)(SEQ ID NO:14)	n.b.	n.b.	n.b.
YpSPTSPS (CTD-S2) (SEQ ID NO:15)	61±6.3	110±26	n.b.
YSPTpSPS (CTD-S5) (SEQ ID NO:16)	30±3.9	34±5.9	> 500
YpSPTpSPS (CTD-S2/S5) (SEQ ID NO:17)	10±0.83	34±6.2	390±82

[a] Errors are deviations from theoretical binding isotherms. All peptides are derived from human proteins except for Pintide. n.b. is used when there is no detectable binding. n.d. stands for not determined. The phosphorylation sites are indicated with a single letter amino acid code and numbered according to sequences appearing in public databases.

Overall architecture. To map the recognition surface of Pin1 for the CTD of hyperphosphorylated Pol IIo, we next carried out structural analysis of Pin1 bound to a phosphorylated heptad repeat of the CTD, N-YpSPTpSPS-C. Crystals of the Pin1-YpSPTpSPS complex were obtained and the structure solved by molecular replacement using the published model of Pin1 (Ranganathan *et al.*, Cell 89:875-886, 1997) and refined to 1.84 Å resolution. The CTD phosphopeptide resides in the cavity separating the PPIase domain from the WW domain. Electrostatic, hydrogen bonding, and van der Waals contacts to residues projecting outward from the concave surface of Pin1's WW domain constitute the Pin1-peptide binding interface (Fig. 1A). No contacts between the bound peptide and the Pin1 PPIase domain are seen in this crystal structure.

Two conformational differences exist in the current Pin1-peptide co-crystal structure relative to the previously reported structure (Ranganathan *et al.*, Cell 89:875-886, 1997). The first change occurs in the PPIase domain. A nearly 70° rotation of the β1-α1 (residues 64-80) catalytic loop results in an exposed PPIase domain active site. Arg-68 and Arg-69, which confer preferential binding of phosphorylated substrates to the Pin1 PPIase domain, now reside well outside of the proline ring binding pocket formed by His-59, Cys-113, Leu-122, Met-130, Phe-134, and His-157 (Figs. 1A-B). While a crystal packing interaction maintains this open active site architecture, the observed orientation of the β1-α1 catalytic loop likely reflects the inherent mobility of this selectivity filter when not engaged with a bound phosphopeptide.

A second conformational change in the Pin1 WW domain results in an exaggerated twist in the β-sheet concurrent with a contraction of the concave WW domain ligand binding surface. The upper third of β2' and β3' together with the β2'/β3' turn moves downward over the amino terminal half of the bound CTD peptide. This movement positions Arg-14 and Phe-25 in van der Waals contact with Pro-3' of the CTD peptide and Ser-32 within hydrogen bonding distance of the backbone carbonyl oxygen of Thr-4' on the CTD peptide. The lower half of the β1' and β2' strands together with their connecting loop pivots upward positioning Ser-16 and Arg-17 for hydrogen bonding to the phosphate on P.Ser-5' of the CTD peptide. The complete phosphate binding module of the Pin1 WW domain encompasses the side chains of Ser-16, Arg-17, and Tyr-23 and the backbone amide of Arg-17. A bound water molecule

mediates the hydrogen bond between Tyr-23 and the serine phosphate. The Tyr-23/Trp-34 aromatic pair spatially defines the pivot point for all of these structural changes.

The aromatic rings of these residues align edge-to-face forming an aromatic clamp which accomodates the backbone atoms of Thr-4' and P.Ser-5' and the ring atoms of Pro-6' of the CTD peptide. Finally, the Ser-7' side chain hydroxyl group forms a hydrogen bond with the protonated indole nitrogen of Trp-34 (Fig. 2A). Tyr-1' and P.Ser-2' of the CTD peptide exhibit a greater degree of flexibility reflected by the weak electron density associated with both of these CTD residues. The entire peptide binds as an extended coil with both P.Ser-Pro peptide bonds in the trans configuration. Modeling of either peptide bond in the *cis* configuration results in significant steric perturbations at the ligand binding interface that would likely result in a loss of peptide binding. This three-dimensional view supports an extended contact surface limited to five consecutive ligand residues with WW domains.

Energetic significance of protein-ligand interactions. To more fully elaborate the WW domain peptide-binding interface quantitatively, the affinities of a limited series of Pin1 mutants for the CTD peptide were measured by fluorescence anisotropy. The results of this analysis are summarized schematically in Figure 3. Replacement of Arg-17 by Ala results in a 6-fold decrease in binding affinity. In R17A Pin1, the remaining hydrogen bonds between the phosphate on Ser-5' and the side-chain hydroxyl group of Ser-16, the backbone amide of Ala-17, and the water-mediated contact with the Tyr-23 hydroxyl moiety provide an interface for low affinity binding of the phosphopeptide. *E. nidulans* Pin1 contains an Asn residue in place of Arg-17 (Fig. 4A). While neutral, the amide side chain at this position can act as a hydrogen bond donor to the P.Ser phosphate. Therefore, WW domains possessing neutral hydrogen bond donors at positions equivalent to 16, 17, and 23 in Pin1 may provide an energetically acceptable interface for P.Ser/P.Thr-Pro recognition. WW4 of the Nedd4-like HECT domain ubiquitin ligase WWP1 contains a conserved Thr-Arg segment homologous to Ser-16 and Arg-17 of Pin1 (Fig. 4A). Binding analysis of isolated WW1, WW3, and WW4 of WWP1 demonstrates phosphorylation-dependent binding only to WW4. Moreover, several HECT domain ubiquitin ligase WW domains including WW3 of Rsp5 contain an equivalent hydrogen-bonding motif (Thr, Asn, and Tyr - Fig. 4A). In addition to the

group IV WW domains, a number of phosphoprotein-binding domains exist including SH2, PTB, STYX, SBF, 14-3-3, and FHA domains (Plowman *et al.*, Proc. Natl. Acad. Sci. USA 96:13603-13610, 1999). While structurally distinct, nearly all such domains utilize Arg residues for the selective recognition of pSer, pThr, and pTyr21,22,23 side chains in a manner analogous to Pin1's WW domain.

Mutations of the other two side chain hydrogen bond donors, Ser-16 and Tyr-23 to Ala and Phe, respectively, each result in a 2.5-fold decrease in binding affinity. Trp-34 constitutes one of two conserved Trp residues found in nearly all WW domains described to date. Together with Tyr-23, this aromatic pair organizes around the Thr-4' and P.Ser-5' backbone, and Pro-6' of the CTD peptide. Replacement of Trp-34 by Phe and Ala cause a 6-fold and 18-fold reduction in binding affinity, respectively. The W34A mutant phenotype is consistent with the reduction of side chain volume leading to less efficient packing of a portion of the CTD peptide backbone and the Pro ring. All Pin1 homologs described to date include one additional residue in the turn linking β1' and β2' (Fig. 4A). This unique structural feature of group IV WW domains may facilitate the conformational change in the β1'/β2' turn that is necessary for the formation of the phosphate binding pocket.

Surprisingly, mutation of Arg-14 and Phe-25, which are predicted to be energetically important based upon the co-crystal structure, results in enhanced binding affinity upon replacement. Structural analysis of the R14A Pin1 mutant without a peptide bound to its WW domain suggests that the WW domain exists in the conformation observed in the current Pin1-phosphopeptide complex rather than that of the wild type unliganded Pin1 complex. The enhanced binding affinity observed for the R14A, F25L, F25V, and F25A mutants might be due in part to preferential stabilization of the peptide-binding WW domain conformation in the absence of ligand.

Comparison with other WW domains. The NMR-derived structure of the YAP65 WW domain complexed with a PPxY-containing peptide had a structurally distinct binding interface from that of the CTD heptide bound Pin1 WW domain (Fig. 4b) (Macias *et al.*, Nature 382:646-649, 1996). While this may reflect distinct mechanisms for ligand recognition by group I and group IV WW domains, the recent

structural analysis of the dystrophin WW domain in complex with a PPxY-containing peptide argues against this (Huang *et al.*, Nature, submitted (2000)). Modeling the peptide bound to YAP65 in a manner similar to that observed in the Pin1-CTD complex results in a peptide orientation superimposed on the extended binding interface observed for Pin1. However, the direction of the polypeptide chain is reversed. This capacity to bind protein ligands in a bi-directional manner is consistent with the dystrophin WW domain structure and is reminiscent of the alternative binding modes utilized by SH3 domains (Kuriyan, J., Cowburn, D., Annu. Rev. Biophys. Biomol. Struct. 26:259-288, 1997). While Pin1 and dystrophin bind their respective ligands in the opposite N- to C-terminal direction, apart from Pin1's ability to bind phosphopeptides, the chemical features of the peptide-binding interface are nearly identical.

The picture that emerges is of a rather limited WW domain contact surface that relies on a set of energetically modest side chain interactions, none of which is absolutely essential for ligand binding. Rather, the summed contributions of this module with ligands spanning five consecutive amino acid residues together with interactions with additional modular domains and longer polypeptide targets likely contribute to target selection in WW domain containing proteins such as Pin1.

While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

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